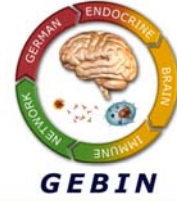




Universitätsklinikum
Regensburg

GEBIN

Regensburg 2013



10th Congress of the GEBIN

(German Endocrine Brain Immune Network)

Regensburg, Germany
University Hospital Regensburg

21st-23rd March 2013

Registration opens December 1, 2012



For more information visit www.gebin.org



Dear Colleagues,

The 10th GEBIN Symposium will be held in Regensburg between March 21st-23rd, 2013.

According to the overall aim of the GEBIN, this meeting will provide an exciting interdisciplinary program covering various fields including anatomy, dermatology, endocrinology, ethology, gynecology, immunology, neurology, pharmacology, psychiatry, psychology, and zoology. The GEBIN meeting is supported by the two International societies: the International Society of Neuroimmunomodulation and PsychoNeuroImmunology Research Society.

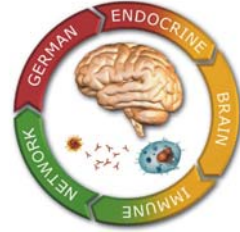
The Symposium will be divided into several thematic sessions. Each session consisting of short oral presentations will be opened with an introductory lecture of an internationally recognized expert in the respective field. All contributions will be published in an issue of *Brain Behavior and Immunity*.

The organizers of the GEBIN Symposium 2013 are proud to offer again an Educational Short Course for students. This course will be held prior to the official start of the GEBIN meeting (March 20 to 21), and it is intended to present aspects of Behavior-Neuro-Endocrine-Immune interactions on a scholarly level.

We would highly appreciate your participation in this exciting meeting and look forward to welcoming you in Regensburg in March 2013.

With kind regards

Rainer H. Straub



Scientific Committee

Prof. Dr. H.O. Besedovsky, Marburg
Prof. Dr. M. Böhm, Münster
Prof. Dr. J. Born, Lübeck
Prof. Dr. A. del Rey, Marburg
PD Dr. H. Engler, Essen
PD Dr. B. Fiebich, Freiburg
PD Dr. U. Gimsa, Dummerstorf bei Rostock
Prof. Dr. R. Gold, Bochum
PD Dr. J. Kraus, Magdeburg
PD Dr. T. Lange, Lübeck
Prof. Dr. N. Müller, München
PD Dr. E. M. Peters, Berlin
Prof. Dr. M. Schedlowski, Essen
PD Dr. M. Schwarz, München
Prof. Dr. V. Stefanski, Hohenheim
Prof. Dr. E. Weihe, Marburg
Prof. Dr. R.H. Straub, Regensburg (Chair)

Local Organizing Committee

Angelika Gräber
Zsuzsa Jenei-Lanzl
Susanne Klatt
Julia Kunath
Torsten Lowin
Madlen Melzer
Georg Pongratz
Luise Rauch
Hubert Stangl
Christine Wolff
and Rainer H. Straub (Chair)

Congress Venue

Educational Short Course: Dollinger Saal im Alten Rathaus, Rathausplatz, 93047 Regensburg
<http://www.regensburg.de/tourismus/tagen-und-feiern/veranstaltungenorte/grosser-dollingersaal/57994>

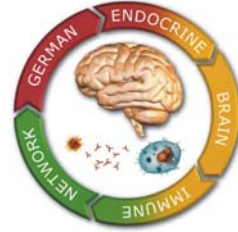
Main Conference: Grand Lecture Hall (Großer Hörsaal) of the University Hospital, F.J.Strauss Allee 11, 93053 Regensburg

Official Language

The official language of the meeting is English.

Registration

Most people already registered in advance via the homepage of the meeting:
http://www.uni-regensburg.de/Fakultaeten/Medizin/Innere_1/aknei/GEBIN2013/index.html



However, some of the participants may register on site during the meeting.
Fee for On-site Registration: 150 Euros

Abstracts

Deadline was 1.12.2012. Abstracts will be published online in *Brain Behavior and Immunity* (IF= 4.720, Editor-in-Chief: Keith W. Kelley), the official journal of the PsychoNeuroImmunology Research Society. Please find the abstracts via URL: <http://dx.doi.org/10.1016/j.bbi.2013.01.074>

Educational Short Course

The GEBIN offers an Educational Course organized by Prof. Dr. Adriana del Rey, Marburg. It is intended to teach basic elements of Behavior-Neuro-Endocrino-Immunology to students.

Time: March 20, 2013, 14:00 – 18:00, and March 21, 2013, 9:00 – 13:00
Venue: Großer Dollingsaal im Alten Rathaus, Rathausplatz, Regensburg

For further details of the course and for registration, please visit the GEBIN homepage: www.gebin.org or contact Adriana del Rey, Dept. of Physiology, Professor at the University of Marburg, e-mail: delrey@mail.uni-marburg.de

Presentations

Most contributions are presented in form of lectures. Please adhere to the following simple rules:
A) number of minutes = number of slides, i.e., 12 min = 10 min lecture (10 slides) + 2 min discussion
B) maximum of result graphs on one slide = 2
C) maximum number of text lines = 7 + one title line

Poster Format: Width = 90 cm x Height = 120 cm

Social Evening

Friday evening, March 22, 2013, from 20:00, in the Salzstadel, Brücksaal, directly at the "Steinerne Brücke", music from Joe Haimerl Band

Hotel Accommodation and Practical Information

See the homepage: <http://www.regensburg.de/tourismus/accommodation/hotels/32359>
Some hotels in the Old Town are: Hotel Goliath, Sorat-Inselhotel, Hotel Bischofshof, Hotel Orphée, Altstadtotel Arch; Hotel near the venue: Apollohotel
It is recommended to take a hotel in the Old Town of Regensburg (near the Regensburg Cathedral). It is easy to travel from the Old Town to the congress venue by bus (line 6 from main station, Fischmarkt, Thundorferstraße, Dachauplatz; sit in the bus until final stop "Klinikum").

Coffee Breaks and Lunch

Coffee, lunch and refreshments will be available in the foyer in front of the Grand Lecture Hall of the University Hospital.



Bus Transfer

There will be no specific bus transfer from downtown to the University Hospital because bus line No. 6 serves perfectly well for this matter. In the two maps on the following pages, the bus stops of bus line No. 6 are indicated by a red dot.

Main Sponsors / Exhibitors

Helga & Erwin Hartl Foundation Regensburg
DGfI - German Society of Immunology (AK NEI)
DFG - German Research Foundation (FOR696)
Biozol Eching Munich
IBL International Hamburg
Salimetrics, Suffolk, U.K.

Supported by

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Deutsche Gesellschaft für Pharmakologie
Deutsche Gesellschaft für Psychologie
Deutsche Gesellschaft für Zoologie

PsychoNeuroImmunology Research Society (PNIRS) and Brain, Behavior & Immunity
International Society of Neuroimmunomodulation (ISNIM)
The European Neuropeptide Club
World Psychiatric Association, Section Immunology and Psychiatry

Acknowledgements

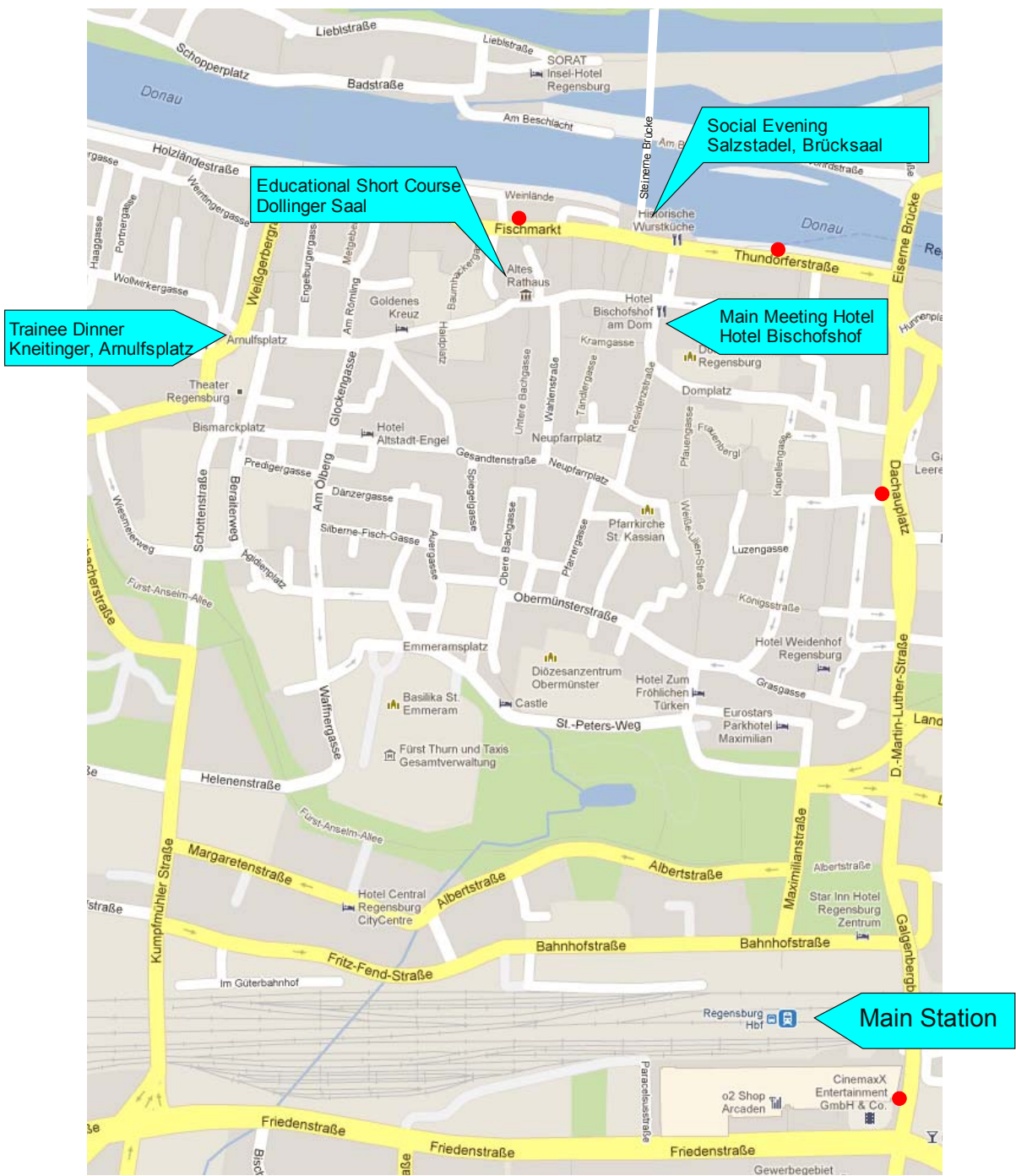
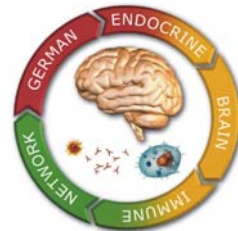
The organizers are grateful for expert assistance to:
Angelika Gräber, Madlen Melzer, Luise Rauch
all from the University Hospital Regensburg, Dept. of Internal Medicine I

Continued Medical Education

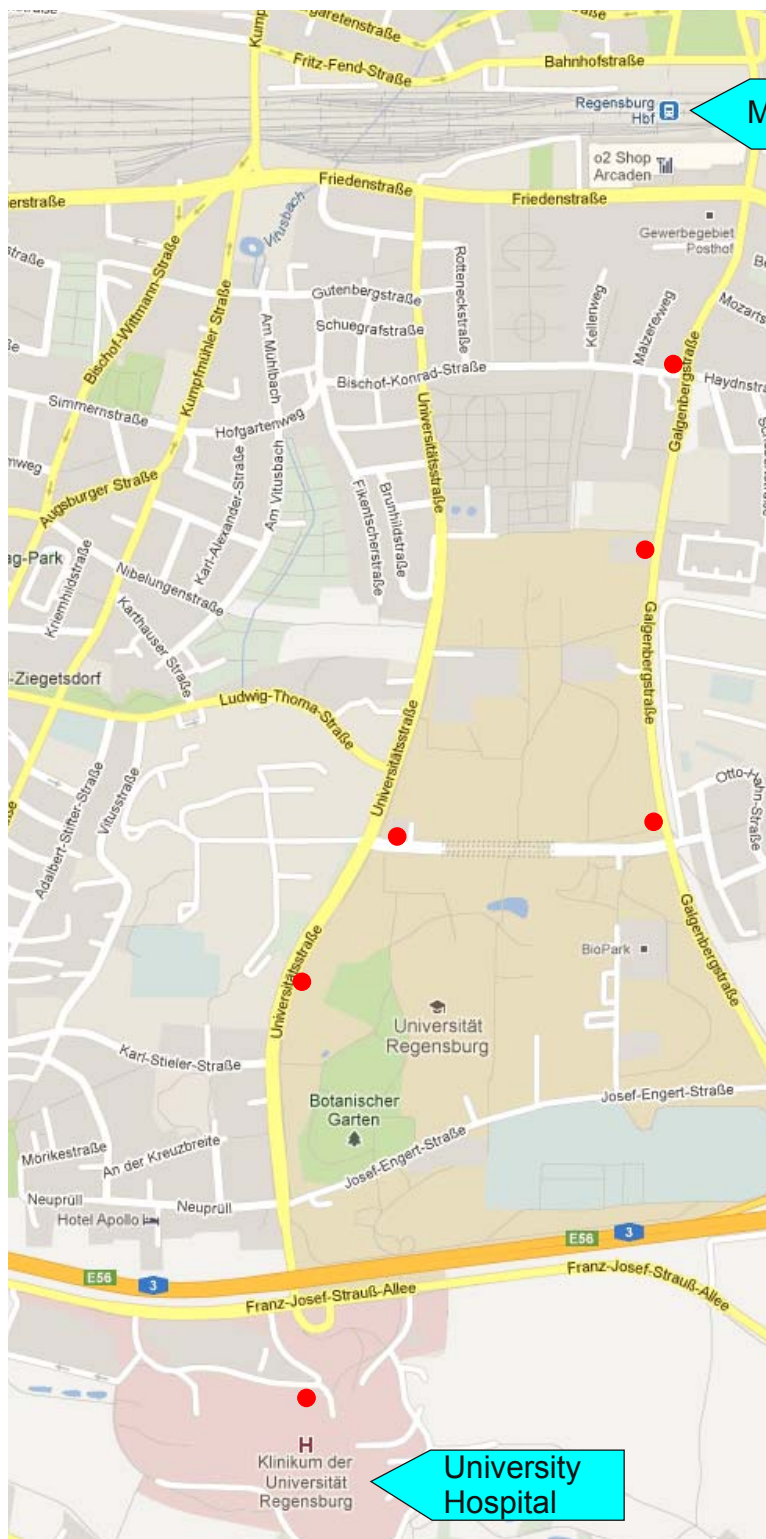
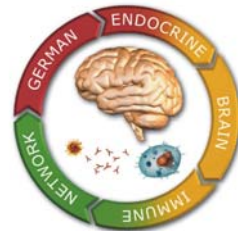
For the entire meeting, one can obtain 12 CME points as approved by the Bayerische Landesärztekammer.

Information

Further information about the GEBIN and the GEBIN 2013 meeting can be found on the GEBIN homepage: www.gebin.org



● Bus Stop of Bus No.6



● Bus Stop of Bus No.6



Program

10th Meeting of the German Endocrine Brain Immune Network

Educational Short Course

Organized by Adriana del Rey, Marburg

together with Hubert Stangl and Julia Kunath, both doctoral students in Regensburg

Wednesday, March 20, 2013

- | | |
|---------------|---|
| 14:00 | Check in |
| 14:15 - 14:30 | Introduction and Students' presentation |
| 14:30 - 15:00 | Immune - neuro - endocrine interactions: the conceptual framework, Adriana del Rey, Marburg |
| 15:00 - 15:45 | Glucocorticoids, microRNAs, and immunomodulation, Simone Kreth, Munich |
| 15:45 - 16:15 | Coffee Break |
| 16:15 - 17:00 | B cell immunity and the peripheral nervous system, Georg Pongratz, Regensburg |
| 17:00 - 18:30 | Students Networking |
| 20:00 | Trainee Dinner (Kneitingen am Arnulfplatz) |

Thursday 21 March (9:00 - 13:00)

- | | |
|---------------|--|
| 9:00 - 9:45 | Chronic stress and immunity, Stefan Reber, Regensburg |
| 9:45 - 10:30 | Alzheimer, aging and Immunity, David Goldeck, Tübingen |
| 10:30 - 11:00 | Coffee Break |
| 11:00 - 11:45 | Sleep and Immunity, Tanja Lange, Lübeck |
| 11:45 - 12:30 | Placebo and immunomodulation, Jan Sebastian Grigoleit, Essen |
| 12:30 - 12:45 | General Discussion and evaluation |

13:00 Departure to GEBIN Meeting

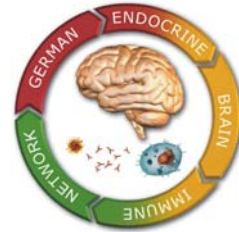
(University Hospital, Franz - Josef - Strauss - Allee 11, 93053 Regensburg)



Main Meeting Program

Thursday, March 21, 2013

- 14:00 – 19:15** **Peripheral Neuroimmune Interactions**
Grand Lecture Hall
Chairs: R.H.Straub, Regensburg, and U. Gimsa, Dummerstorf
- 14:00 – 14:15 Address of Welcome, *R.H. Straub*, Regensburg
- 14:15 – 15:00 **Neural circuitry in immunity**
Kevin J. Tracey
Feinstein Institute for Medical Research, Manhasset, NY
- 15:00 – 15:12 Neuroimmunomodulation in the pathogenesis of endometriosis
C. Arellano Estrada, Berlin
- 15:12 – 15:24 Blockade of the neuropilin-2/plexin A2 receptor - a new therapeutic approach
towards rheumatoid arthritis?
J. Kunath, Regensburg
- 15:24 – 15:36 TRPV1-dependent hyperalgesia in peritoneal endometriosis
M. L. Barcena de Arellano, Berlin
- 15:36 – 15:48 Neuroimmune interactions after nerve injury and opioid-mediated pain control,
M. Ö. Celik, Berlin
- 15:48 – 16:00 Is IL-17 causally involved in the proinflammatory role of the sympathetic
nervous system?
M. Ebbinghaus, Jena
- 16:00 – 16:12 KdPT: novel protective role against impaired wound healing in diabetes?
P. Gkogkolou, Münster
- 16:15 – 16:45** **COFFEE BREAK**
- Chairs: E.M. Peters, Berlin and U. Gimsa, Dummerstorf
- 16:45 – 16:58 Disruption of the estrogen-dependent sympathetic nerve fibers remodelling in
adenomyosis uteri
M. L. Barcena de Arellano, Berlin
- 16:58 – 17:00 5-HT₃ receptor expression in primary human monocytes
A. Kumar, Freiburg



- 17:00 – 17:12 Regulation of the β -endorphin precursor proopiomelanocortin in lymphocytes in a rat model of inflammatory pain
Santhosh Chandar Maddila, Berlin
- 17:12 – 17:24 A feedback loop involving microRNA regulates opioid- and cannabinoid-functions
N. Schneevogt, Magdeburg

The Neuro – Rheumatologic / Orthopedic Session

Sponsored by the DFG Research Unit FOR696
Supported by the Helga & Erwin Hartl Foundation Regensburg

Chairs: S. Grässel, Regensburg, and G. Pongratz, Regensburg

- 17:24 – 17:36 The endocannabinoid anandamide modulates adhesion, proliferation and the production of inflammatory mediators in rheumatoid arthritis synovial fibroblasts
T. Lowin, Regensburg
- 17:36 – 17:48 Neuroendocrine mediators regulate production of B cell activating factor of the tumor necrosis factor family (BAFF) in human synovial fibroblasts
G. Pongratz, Regensburg
- 17:48 – 18:00 Modulation of inflammatory cytokine release by hypoxia mediated tyrosine hydroxylase induction in mixed synovial cells of patients with rheumatoid arthritis and osteoarthritis
Z. Jenei-Lanzl, Regensburg
- 18:00 – 18:12 The Spatial Energy Expenditure Configuration and Possible Applications in an Experimental Model of Arthritis
S. Klatt, Regensburg
- 18:12 – 18:24 The peripheral nervous system and focal bony erosions in arthritis
H. Stangl, Regensburg
- 18:24 – 18:36 The role of norepinephrine in adult human articular chondrocytes
J. Lorenz, Regensburg
- 18:36 – 18:48 The role of substance P and noradrenaline in fracture callus differentiation
T. Niedermair, Regensburg
- 18:48 – 19:00 Collagen-induced arthritis impairs osteoclastogenesis and reactivity to sympathetic neurotransmitter stimuli in bone marrow-derived macrophages from DA rats
D. Muschter, Regensburg
- 19:00 – 19:12 Inadequate glucocorticoid secretion in experimental arthritis in rats is closely linked to impaired mitochondria and reduced lipid breakdown in the adrenal cortex
C. Wolff, Regensburg

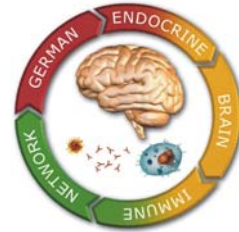


19:12 – 19:24 Toll-like receptor pathway in schizophrenia – a pilot study
E. Weidinger, München

19:30 – 21:30 RECEPTION und Poster Session, Foyer in front of Grand Lecture Hall

- 1) Effects of mineralocorticoid receptor signaling during sleep on the expression of CD62L and CCR7 on naïve T cells
L. Besedovsky, Tübingen
- 2) Quantifying the number and affinity of glucocorticoid receptors in porcine peripheral blood mononuclear cells – establishment of a ligand binding assay
L. Engert, Hohenheim
- 3) Recovery of the immune system after hibernation in an obligate hibernator, the edible dormouse
N. Havenstein, Hohenheim
- 4) Reactivity and cytokine production of T-cells in pregnant sows housed in dynamic groups or single crates
C. Schalk, Hohenheim
- 5) Immunomodulation of angiogenic factor production in pituitary tumor cells under basal and hypoxia mimicking conditions
K. Lucia, Munich
- 6) CSF outflow along spinal nerves – a neuroradiological document
K. Bechter, B. Schmitz, Guenzburg

19:30 – 20:15 Meeting of the Steering Committee of the GEBIN
Small Lecture Hall



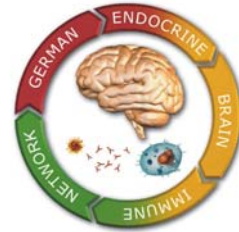
Friday, March 22, 2013

09:00 – 12:30 Neuroendocrinology and Immune Function

Grand Lecture Hall

Chairs: M. Böhm, Münster, and T. Lange, Lübeck

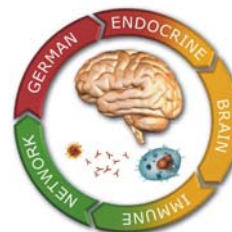
- 09:00 – 09:45 **What's bugging you? Infection history as an unmeasured confound in psychoneuroimmunology**
Jos Bosch
Department of Clinical Psychology, University of Amsterdam
- 09:48 – 10:00 The role of estrogen and ER α/β in the sensory and sympathetic nerve fiber imbalance in peritoneal endometriotic lesions
J. Arnold, Berlin
- 10:00 – 10:12 Higher basal interleukin-6 and cortisone levels in poor sleeping pregnant women but not in poor sleeping young mothers
C. Berndt, Dresden
- 10:12 – 10:24 Synovial fibroblasts are novel target cells for the melanocortin peptide α -melanocyte-stimulating hormone
M. Böhm, Münster
- 10:24 – 10:36 A new role of the oxytocin system in human skin stress responses and implications for atopic dermatitis
V. Deing, Hamburg
- 10:36 – 10:48 The chondroprotective role of the melanocortin system in murine osteoarthritis
G. Hackmayer, Regensburg
- 10:48 – 11:00 Alterations in diurnal cortisol secretion, cognitive performance and frailty in an aging population: preliminary results of the KORA Age 1 Study
H. Johar, München
- 11:00 – 11:30 COFFEE BREAK**
- 11:30 – 11:42 Effects of mifepristone on T cell subsets in humans
T. Lange, Lübeck
- 11:42 – 11:54 Influence of CYB5A gene variants on risk of rheumatoid arthritis and local endocrine function in the joint
K. Stark, Regensburg
- 11:54 – 12:06 Analyzing the microarray mRNA profile of graying human hair follicles: a promising approach in stress and aging research
E.M.J. Peters, Berlin
- 12:06 – 12:18 Neural noradrenergic control of experimental Chagas' disease
E. Roggero, Rosario, Argentina



- 12:18 – 12:30 Functional stress response in patients with rheumatoid arthritis: Impact of genetic factors
O. Malysheva, Leipzig
- 12:30 – 13:30 LUNCH**
Foyer in front of Grand Lecture Hall
- 13:30 – 17:30 Stress, Behavior, and Immune Function**
Grand Lecture Hall
Chairs: V. Stefanski, Hohenheim, and H. Engler, Essen
- 13:30 – 14:15 **Ecohealth: Immunogenomics in Wildlife Populations**
Simone Sommer
Evolutionary Genetics, Leibniz Institute for Zoo and Wildlife Research, Berlin
- 14:18 – 14:30 Biological and psychological predictors of visceral pain sensitivity in healthy women
S. Benson, Essen
- 14:30 – 14:42 Does repeated anticipation induce neuroendocrine modulation of the immune system in domestic pigs?
J. Brietzke, Dummerstorf
- 14:42 – 14:54 Adoptive transfer of CD4⁺ mesenteric lymph node cells from mice exposed to chronic psychosocial stress: physiological and immunological consequences
P. Gross, Regensburg
- 14:54 – 15:06 Influence of housing on endocrine function and immune system in pregnant sows
V. Grün, Hohenheim
- 15:06 – 15:18 Maternal prenatal life events increase risk for atopic disorders in children
I.R.V. Hartwig, Hamburg
- 15:18 – 15:30 Stress related modulation of glucocorticoid sensitivity and T cell responses in human pregnancy
E. Ludwigs, Hamburg
- 15:30 – 15:42 Changes in the systemic immune status following chronic psycho-social stress exposure in male mice
T. Thi Thu Nguyen, Regensburg
- 15:42 – 15:54 Mediation of the extinction process in behaviorally conditioned immunosuppression
K. Orlowski, Essen
- 15:54 – 16:06 Is TH17 immunity altered by chronically perceived stress?
E.M.J. Peters, Berlin



- 16:06 – 16:18 Stress-induced local inflammation correlates with an increase in inflammatory myeloid cells
D. Schmidt, Regensburg
- 16:18 - 16:30 Placebo responses in patients with house dust mite allergy
S. Vits, Essen
- 16:30 – 17:00 COFFEE BREAK**
- Chairs: V. Stefanski, Hohenheim, and H. Engler, Essen
- 17:00 – 17:12 Allostatic Load as a Stress Marker in MONICA/KORA
S. Weber, München
- 17:12 – 17:24 Placebo-induced immunosuppression in humans: role of learning and expectation
L. Wendt, Essen
- 17:30 – 19:20 Neuroimmunology & Neuroinfectiology in the CNS**
Grand Lecture Hall
- Chairs: E. Weihe, Marburg, and H.O. Besedovsky, Marburg
- 17:30 – 18:15 **Neuropeptide transmission and stress signaling: Role of PACAP in the adrenal gland and hypothalamus**
Lee Eiden
Section on Molecular Neuroscience, Laboratory of Cellular and Molecular Regulation, National Institute of Mental Health, Bethesda, MD
- 18:18 – 18:30 Inhibition of Toll-like receptor 4 (TLR4)-induced NF- κ B activation by NOPr is lost in human glioblastoma cells chronically exposed to LPS
A. Bedini, Bologna, Italy
- 18:30 – 18:42 Experimental endotoxemia as a model to study neuro-immune mechanisms in human visceral and somatic pain
S. Benson, Essen
- 18:42 – 18:54 Experimental endotoxemia as a model to study somatic pain sensitivity in humans
A. Wegner, Essen
- 18:54 – 19:06 A cytokine network in the brain during synaptic plasticity and learning
A. del Rey, Marburg
- 19:06 – 19:18 ACE2 drives dendritic cell function and neuroantigen specific immune responses
A. Kovacs, Erlangen
- 20:00 Banket Evening**
in the Salzstadel, Brücksaal, near the “Steinerne Brücke”



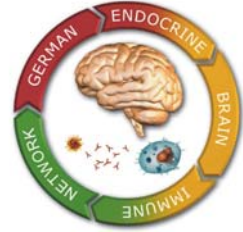
Saturday, March 23, 2013

09:30 – 12:35 Neuroendocrine Immune Network in Psychiatric Disease

Grand Lecture Hall

Chairs: N. Müller, München, and B. Fiebich, Freiburg

- 09:30 – 10:16 **Autoantibodies in patients with psychiatric disturbance**
Angela Vincent
Neuroimmunology Group, Nuffield Department of Clinical Neurosciences,
University of Oxford, U.K.
- 10:16 – 10:28 Updating the mild encephalitis hypothesis of schizophrenia
K. Bechter, Günzburg
- 10:28 – 10:40 Peripheral effects of central serotonin depletion in a mouse model for sub
sickness behavior
D. Beis, Berlin
- 10:40 – 10:52 Impact of the immunosuppressant rapamycin on amygdala activity and
behavior
K. Bösche, Essen
- 11:00 – 11:30 COFFEE BREAK**
- Chairs: N. Müller, München, and B. Fiebich, Freiburg
- 11:30 – 11:42 Depression und its determinants in patients with rheumatoid arthritis
H. Morf, Leipzig
- 11:42 – 11:54 CCL17 deficiency is associated with beneficial CNS immune responses and
prevents cognitive decline in a mouse model of Alzheimer's disease
J. Alferink, Münster
- 11:54 – 12:06 Quantitative analysis of the kynurenine pathway
G.A. Schütze, München
- 12:06 – 12:18 The anti-inflammatory effects of the 5-HT₃ receptor antagonist tropisetron are
mediated by the inhibition of p38 MAPK activation in primary human monocytes
H. Bhatia, Freiburg
- 12:18 – 12:30 Toll-like receptor pathway in schizophrenia – a pilot study
E. Weidinger, München
- 12:30 – 12:35 Closing remarks of the GEBIN spokesman
V. Stefanski, Hohenheim
- 12:35 Fin of the GEBIN Meeting



Abstracts

of the

10th Meeting of the

German Endocrine Brain Immune Network

(GEBIN)

Regensburg, Germany

March 20-23, 2013



Peripheral Neuroimmune Interaction

Neuroimmunomodulation in the pathogenesis of endometriosis

C. Arellano Estrada, ML. Barcena de Arellano, A. Schneider, and S. Mechsner

Endometriosis Research Centre, Department of Gynecology, Charité - Universitätsmedizin,
Berlin, Germany

Endometriosis (EM) is a disease characterized by chronic inflammation, mostly causing pelvic pain, though the pain pathogenesis remains unknown. Nevertheless, EM-associated nerve fibers (NF) seem to play a crucial role. Recent studies evidenced an imbalance between sympathetic and sensory NF, leading to higher levels of pro-inflammatory neurotransmitters (NT) and lower levels of anti-inflammatory NT, the mechanisms modulating this irregularity remain undisclosed. Semaphorins (semas) are nerve repellent factors, better known as axon guidance molecules. Particularly class-3 semas are known to guide sensory and/or sympathetic nerve growth cones. A sema-dependent sympathetic NF depletion could be demonstrated in various chronic inflammatory diseases including rheumatoid arthritis. Purpose of the study was to define the role of semas in the modulation of sympathetic NF in EM.

Therefore the expression pattern of different semas and their receptors was defined in peritoneal endometriotic lesions (pEL) and healthy peritoneal tissue (HP). In addition, the presence of macrophages in pEL and HP was analyzed, in order to determine a potential interaction with semaphorins.

pEL showed a significant upregulation of semas, the receptors were identified in stroma and epithelial cells of the pEL as well as in sympathetic NF. Analysis of the macrophages revealed an expression of semas in EM-associated macrophages.

These results suggest that the chronic pro-inflammatory reaction in EM, which induces a macrophages release, is crucial for its pathogenesis, whereas EM-associated macrophages expressing the nerve repellent factors are potentially involved in the depletion of sympathetic NF, leading to an impairment of anti-inflammatory NT and supporting the chronic inflammation in EM.

Please find the abstracts via URL: <http://dx.doi.org/10.1016/j.bbi.2013.01.074>



Disruption of the estrogen-dependent sympathetic nerve fibers remodelling in adenomyosis uteri

Maria Luisa Barcena de Arellano^a, Jeannette Oldeweme^a, Achim Schneider^a, and Sylvia Mechsner^a

^a Endometriosis research centre, Clinic for Gynaecology, Charité - Universitätsmedizin Berlin, Berlin, Germany.

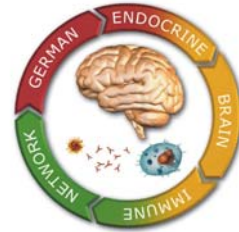
In rodents, the sympathetic innervation is depleted in estrogen-rich phases of the cycle and restored in estrogen-poor phases. A decrease of PGP-9.5-positive nerve fibers (NF) at the endometrial-myometrial interface of adenomyosis (AM) is described. However, NF are present in some AM samples, suggesting a dysfunctional regulation of hormone-dependent changes in uterine innervation in AM.

In order to investigate the estrogen-dependent remodeling of uterine innervation in AM, we characterized sympathetic NF in 42 AM specimens by using immunohistochemistry. Furthermore, we analyzed the interaction of sympathetic NF and estrogen receptor α and β in AM patients.

The myometrium of women with AM showed less sympathetic NF than the control group ($p < 0.01$). The control group showed less sympathetic NF in the secretory than in the proliferative phase. In AM we could not find a cycle-dependent modulation of sympathetic NF. The double staining showed an expression of estrogen receptor α and β in sympathetic NF. In healthy myometrium; a cycle-dependent modulation of the innervation was seen, but in AM it seems to be disturbed.

This study demonstrated a reduction of sympathetic myometrial NF in AM. The sympathetic outgrowth is reduced in rodents during estrogen-rich phases, suggesting that estrogen modulates the sympathetic innervation. We could demonstrate an estrogen receptor α and β expression by sympathetic NF, suggesting an estrogen-dependent depletion of sympathetic NF. The uterus seems to go through an estrogen-dependent remodeling. In AM, this remodeling seems to be disturbed since we were able to demonstrate a reduction of sympathetic NF in all cycle phases.

Please find the abstracts via URL: <http://dx.doi.org/10.1016/j.bbi.2013.01.074>



TRPV1-dependent hyperalgesia in peritoneal endometriosis

Maria Luisa Barcena de Arellano^a, Nina Pauly^a, Achim Schneider^a and Sylvia Mechsner^a

^a Endometriosis research centre, Clinic for Gynecology, Charité – Universitätsmedizin Berlin, Berlin Germany

About 40% of the women with chronic pelvic pain suffer from endometriosis (EM). The chronic inflammatory condition in EM is accompanied with an imbalance of sensory and sympathetic peritoneal nerve fibers, with a hyperinnervation of sensory NF and a hypoinnervation of sympathetic NF close to peritoneal endometriotic lesions (pEL). However, the pro-inflammatory stage of EM does not correlate with the pain severity, suggesting that other inflammatory and/or pain mediators co-modulate the pain sensation in EM.

The presence of the TRPV1 in the pEL using immunohistological analysis was examined. Neural PC12 cells were incubated with peritoneal fluid (PF) from women with and without EM and the amount of TRPV1-RNA and protein was evaluated.

Close to the lesion, the density of TRPV1-positive NF was higher than in healthy peritoneum ($p < .001$). The density of TRPV1-positive NF was increased in the pEL with pain in comparison to pEL without pain ($p < .05$).

The relative TRPV1-RNA level was higher in cells incubated with PF from women with EM ($p < .05$). Only the symptomatic EM group showed a band in the western blot analysis.

This study confirmed an increase in TRPV1-positive NF in pEL, suggesting that TRPV1 plays a crucial role in the pain transmission in EM. Furthermore, an overexpression of the TRPV1- RNA and protein level in PC12 incubated with PF from women with EM was demonstrated, suggesting that the PF from women with EM expresses mediators that induce the expression of TRPV1 in pEL.

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Neuroimmune interactions after nerve injury and opioid-mediated pain control

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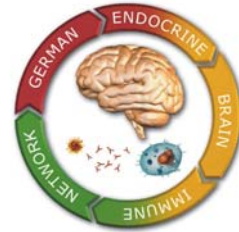
Here, we investigated pain relief resulting from neuroimmune interactions associated with peripheral nerve damage. Our hypothesis is based on a new concept that activation of opioid receptors on immune cells leads to the release of opioid peptides, which activate neuronal receptors, to improve neuropathic pain.

As a model of neuropathy we applied chronic constriction injury of the sciatic nerve in mice. Mechanical sensitivity was evaluated with von Frey filaments. Immune cells infiltrating damaged nerves were isolated 2 days following the injury, and the secretion of opioid peptide Met-enkephalin was examined using radioimmunoassay.

In vivo we found that selective agonists of mu-, delta- and kappa-opioid receptors injected at the nerve injury site produced analgesia. This effect was attenuated when immune cells infiltrating damaged nerves were depleted. In vitro, the opioid receptor agonists dose-dependently secreted Met-enkephalin from leukocytes. This release was abrogated by the respective opioid receptor antagonists, by blocking G α i and G β γ subunits, phospholipase C, and inositol 1,4,5-trisphosphate receptors, and by removing Ca²⁺ from intracellular, but not extracellular, stores.

Our results suggest that activation of leukocytic G α i-coupled opioid receptors induces Ca²⁺-regulated secretion of endogenous opioid peptides, which might contribute to the amelioration of neuropathic pain. These findings provide mechanistic evidence supporting the idea that damaged peripheral nerves infiltrated by opioid-containing immune cells might be a promising target for the control painful inflammatory neuropathies.

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Is IL-17 causally involved in the proinflammatory role of the sympathetic nervous system?

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The proinflammatory cytokine Interleukin 17 (IL-17) is considered an important mediator of inflammation in several autoimmune diseases. It is secreted by immune cells such as Th17 cells, and its receptors are ubiquitously expressed. Recently we observed in the model of murine antigen-induced arthritis (AIA) that the anti-inflammatory and the anti-nociceptive effect of sympathectomy was accompanied by a significant reduction of Th17 responses (Ebbinghaus et al., *Ann Rheum Dis* 2012;71:253-261). This raised the question whether IL-17 is a major player in neuro-immune interactions in murine AIA.

In order to further elucidate the role of IL-17 in AIA and in the proinflammatory effect of the sympathetic nervous system, we performed several experiments in AIA using IL-17 knockout mice, a neutralizing anti-IL-17-antibody and adrenoceptor agonists.

We found that destruction of sympathetic neurons (by chemical sympathectomy) in the absence of IL-17 still acts anti-inflammatory in AIA. Furthermore neutralization of IL-17 in wild-type C57Bl/6 mice did not effectively reduce joint swelling but significantly reduced secondary mechanical hyperalgesia and attenuated gait abnormalities of the ipsilateral hind limb in the acute stage of inflammation. In addition treatment of AIA-derived lymphocytes *ex vivo* with α - or β -adrenoceptor agonists did not change their ability to produce IL-17 following re-stimulation with the antigen.

Taken together we found that IL-17 alone is not the major player in AIA. Furthermore we did not obtain evidence that IL-17 is causally involved in the proinflammatory effect of the sympathetic nervous system. Nonetheless we found a robust involvement of IL-17 in inflammation-evoked mechanical hyperalgesia.

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KdPT: novel protective role against impaired wound healing in diabetes?

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Diabetic ulcers are a major and therapeutic challenging complication in diabetes. Not only increased morbidity of affected patients but also extremely high costs on health care systems make the development of new therapeutic strategies an urgent necessity. Our group works on the pluripotent protective effects of melanocortin peptides in various inflammatory models. In this work, the effects of high glucose on keratinocytes and the protective effects of KdPT, a melanocortin derivative, against glucotoxicity, were investigated.

High glucose adversely affected various vital cell functions, e.g. proliferation, metabolic activity, viability and migration. No significant induction of apoptosis or autophagy was observed. Using atomic force microscopy studies we showed that high glucose profoundly changes the cells' biomechanical properties (diameter, elasticity). Induction of intracellular oxidative stress and endoplasmic reticulum stress mediated glucotoxicity. KdPT, a truncated tripeptide of alpha-MSH, significantly attenuated high glucose induced oxidative stress and antagonised the toxic effects of glucose on cell viability, metabolic activity and migration. Finally, using an ex vivo model of skin organ cultures we validated our in vitro generated data in a more physiological environment.

In summary, our work creates a basis for better understanding the mechanisms of impaired wound healing in diabetes and possibly points towards novel therapies for diabetic ulcers.

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Modulation of inflammatory cytokine release by hypoxia mediated tyrosine hydroxylase induction in mixed synovial cells of patients with rheumatoid arthritis and osteoarthritis

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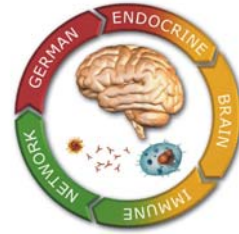
The microenvironment of inflamed joints is hypoxic and hypoxia has been shown to induce tyrosine hydroxylase (TH) *in vivo*. In previous studies, we detected TH-positive, catecholamine-producing cells in inflamed synovial tissue. Therefore, the aim of our study was to investigate the influence of hypoxia induced catecholamines on inflammatory responses in arthritis.

Synovial cells of rheumatoid arthritis (RA) and osteoarthritis (OA) patients were isolated by enzymatic digestion and cultivated under normoxia or hypoxia. For determination of TH-mediated effects, cells were incubated with the competitive TH-inhibitor alpha-methyl-p-tyrosine (α MPT). In addition, different concentrations of catecholamine receptor agonists or antagonists were applied. Furthermore, cofactors required for optimal TH activity were used. After 24 hours, cells were stained for TH, concentrations of released cytokines and catecholamines were quantified in supernatants.

Hypoxia increased the number of TH-positive cells compared to cells cultured under normoxia. Hypoxia inhibited IL-6, IL-8, and IL-10, whereas TNF was unaffected in OA. In contrast, hypoxia increased IL-6 and IL-8, but inhibited IL-10 and TNF in RA. TH blockade by α MPT reversed hypoxia-induced effects. Specific receptor antagonists were able to reverse hypoxia-induced influences. TH cofactors such as iron (Fe) stimulated hypoxia-induced effects on TNF. HPLC measurements showed low catecholamine concentrations.

This study demonstrates that hypoxia induces TH expression and inhibits TNF in synovial cells, especially in RA patients. In summary, these results suggest that hypoxia influences the inflammatory response in RA synovial cells. In current experiments, we test the effect of adoptively transferred TH-positive cells in mice with collagen type II-induced arthritis.

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The Spatial Energy Expenditure Configuration and Possible Applications in an Experimental Model of Arthritis

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An autoimmune response with differentiation and proliferation of immune cells and the subsequent tissue-directed inflammatory process in the symptomatic phase of the disease are very energy-demanding. As recent calculations demonstrate, the activated immune system needs approximately 25% of the basal metabolic rate. We hypothesized that during chronic long-standing inflammatory diseases like experimental arthritis, a reallocation of energy-rich fuels to the activated immune system is necessary in order to nourish the inflammatory process.

Energy consumption and, thus, ATP generation can be measured by studying the consumption of oxygen, which was carried using optical oxygen microsensors (PreSens, Regensburg, Germany).

A new technique termed “spatial energy expenditure configuration (SEEC)” was developed to demonstrate bodily areas of high energy demand. SEEC is based on removal of tissue during the course of experimental arthritis, and subsequent determination of oxygen consumption in cells and tissue. For this purpose, small weighed pieces of the respective organ with a size of 4 mm are placed in 24-well multidishes with integrated oxygen sensors, which allows for non-invasive detection of oxygen consumption *in vitro*. The value is given in $\mu\text{mol O}_2/\text{h}$ and refers to 4 mm sized pieces as percentage of mouse weight.

Concerning the draining lymphoid nodes, we were able to observe a marked increase in oxygen consumption of 200% during the course of arthritis. Other investigated organs like liver or kidney decreased their oxygen consumption (control vs. arthritic animals). To further test the applicability of the new method, experiments with an agonist at the cold receptor TRPM-8 were started. Agonists at this receptor induce a cold response, and energy expenditure in the different organs tested and course of arthritis might change.

The SEEC technique enables us to identify locations of high energy demand that are involved in the initiation and continuation of the autoimmune process in an animal model of arthritis.

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5-HT₃receptor expression in primary human monocytes

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There is evidence that 5-hydroxytryptamine-3 (5-HT₃) receptor antagonists may be useful for treatment of inflammatory disorders. Studies from human and animal research showed that 5-HT₃ receptor antagonists, particularly tropisetron, exert analgesic and anti-inflammatory activity. We have demonstrated that tropisetron inhibited the release of inflammatory mediators such as tumor necrosis factor (TNF) in primary human monocytes. So far, the underlying mechanisms of these effects have not been investigated in detail. This is especially true for the role of the 5-HT₃ receptor subtypes A,B,C,D,E in inflammatory events.

Here, we investigated the effects of tropisetron and lipopolysaccharide (LPS) on the expression of 5HT₃ receptor A,B,C,D,E mRNA levels by real time PCR and FACS analysis.

Our data indicate that the different 5-HT₃ receptor subtypes are modulated at its transcriptional and surface expression level by inflammatory conditions and 5-HT₃ antagonists such as tropisetron in primary human monocytes.

5-HT₃ receptor antagonists are therefore a new and promising therapeutic option. New and more selective – in respect to the 5-HT₃ subtypes – 5-HT₃R antagonists might be a future perspective in the pharmacological treatment of inflammatory diseases such as rheumatoid arthritis.

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Blockade of the neuropilin-2/plexin A2 receptor

- a new therapeutic approach towards rheumatoid arthritis? -

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The loss of sympathetic nerve fibers (SNF) is a general principle in inflammatory diseases. Since sympathetic neurotransmitters exert anti-inflammatory effects at increased concentrations, their loss in inflamed and infected tissue is reasonable to overcome infection. However, this mechanism is unfavourable in chronic inflammation like rheumatoid arthritis (RA). Semaphorins are major factors involved in axon guidance and repulsion mediated by a neuropilin-2/ Plexin A2 receptor complex on nerve endings. We hypothesize that antagonizing semaphorin binding to its receptor can keep nerve fibers in the inflamed area, and this may be a new therapeutic principle in the treatment of RA. In this study, we wanted to test the neutralizing effects of polyclonal antibodies to plexin A2 on semaphorin 3F-induced nerve fiber repulsion.

For these investigations, a neurite outgrowth assay was used to study the behaviour of nerve fibers from sympathetic trunk ganglia of postnatal mice.

Nerve repulsion caused by semaphorin 3F is about 35-50%. Repulsion can be completely abrogated by a polyclonal anti-plexin A2 antibody in a concentration of 157 nmol/l (to 0-9%; $p < 0.005$). Similarly, an antibody against neuropilin-2 can also abrogate repellent factor-induced repulsion. Presently, we introduce a phage display technology to identify the oligopeptide structure of the antigenic antibody binding site. A total of 14 peptides might represent possible candidates for binding, which is presently tested.

This study provided us with a first important tool to manipulate sympathetic nerve fiber repulsion. We are testing these antibodies in an animal model of experimental arthritis.

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The role of norepinephrine in adult human articular chondrocytes

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Norepinephrine (NE) belongs to the catecholamine family of tyrosine-derived neurotransmitters of the sympathetic nervous system. Tyrosine-hydroxylase positive sympathetic nerve fibers have been identified in bone marrow, in the periosteum, and in bone-adherent ligaments indicating that growth and metabolic activity of bone and joint tissues is regulated by sympathetic neurotransmitters. It is known that NE can regulate cell proliferation or apoptosis in several cell types, such as osteoblasts. It is further described that NE modulates inflammation during rheumatoid arthritis and gut inflammation. Here, we aim to understand the role of NE in human osteoarthritic chondrocytes with regard to inflammation and its impact on metabolic activity.

Human chondrocytes were isolated from post-surgery discarded human osteoarthritic articular cartilage. Expression of adrenergic receptor on articular cartilage chondrocytes was tested with standard end point PCR and immunohistochemical analysis. Employing 3D cell cultures in fibrin gel, effects of NE on IL-1 β induced gene expression of pro-inflammatory cytokines and matrix metalloproteinases (MMP) were analyzed with quantitative real-time PCR. The impact of NE on cell proliferation was determined in monolayer culture with BrdU ELISA and FACS analyses, the effect on apoptosis with Caspase 3/7 ELISA. To test the adrenergic receptor involved in apoptosis or proliferation, the α 1-adrenergic receptor antagonist doxazosin, the α 2-adrenergic receptor antagonist yohimbine, and the β 1/2/3-adrenergic receptor antagonist nadolol were included in BrdU/caspase-3/7-ELISAs.

Chondrocytes cultured in monolayer and in 3D under non- and inflammatory conditions expressed α 1D-, α 2A/B/C- and β 2-adrenergic receptors. β 2-adrenergic receptors were detected on protein level in human osteoarthritic cartilage as well. Stimulation with NE has significantly reduced IL-1 β induced gene expression of IL-8 and MMP-13 in human osteoarthritic chondrocytes cultured in 3D fibrin gel. Notably, we were unable to detect an impact on IL-1 β induced gene expression of interleukin-6, MMP-2 and MMP-3. Furthermore, NE inhibits BrdU incorporation compared to the controls. This effect was reversed by nadolol. In cell cycle analyses, we showed that NE increased the G1/G0-phase population and decreased S-phase population. Additionally, we observed an increase of caspase-3/7 activity after NE treatment that was reversed after addition of α 1-adrenergic receptor antagonist doxazosin.

Neurotransmitters of the sympathetic nervous system like NE presumably mediate an anti-inflammatory / chondroprotective effect in human osteoarthritic chondrocytes via reducing IL-1 β induced IL-8 and MMP-13. Furthermore, NE is able to modulate the metabolic activity of chondrocytes by a cell cycle slow-down via β 2-adrenergic receptor signaling and by induction of apoptosis via α 1D-adrenergic receptor signaling. We therefore assume a yet unknown function of catecholaminergic neurotransmitters in adult human cartilage that might have an impact on osteoarthritis pathology.

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The endocannabinoid anandamide modulates adhesion, proliferation and the production of inflammatory mediators in rheumatoid arthritis synovial fibroblasts

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In rheumatoid arthritis (RA), synovial fibroblasts (SF) secrete large amounts of IL-6, IL-8 and several matrix metalloproteinases, which are crucial for cartilage destruction. RASF are sensitive to the action of cannabinoids and they express cannabinoid receptors type I and II (CB₁ and CB₂) as well as endocannabinoid degrading enzymes. Cannabinoids are regarded as antiinflammatory and since anandamide is found in RA synovial fluid we investigated how this endocannabinoid affects adhesion, proliferation and the production of inflammatory mediators of RASF.

Adhesion was assessed by the XCELLigence system (Roche). Proliferation was quantified by the amount of incorporated fluorescent dye into cellular DNA. MMP-3 and cytokines were detected by ELISA. Cannabinoid receptors were visualized by immunofluorescence.

Anandamide slightly decreased the production of IL-6, IL-8 and MMP-3 by a non-cannabinoid receptor mediated mechanism. Anandamide increased adhesion of SFs in a CB₁-dependent manner and decreased proliferation, which was blocked by inhibiting cyclooxygenase-2. Furthermore, proliferation was negatively correlated with CB₁ expression. In addition, GPR18 and GPR55, two recently orphanized cannabinoid receptors, which might serve as target for anandamide, were detected in SFs.

Anandamide promotes an antiinflammatory phenotype in RASFs by activating several receptors. Additionally, cyclooxygenase-2 metabolites of anandamide exert their anti-proliferative effects independent of CB₁ and CB₂. The identification of GPR18 and GPR55 in RASFs demonstrates novel sites of action for anandamide and its metabolites and provide attractive targets for future therapeutics to be applied to patients with RA.

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Regulation of the β -endorphin precursor proopiomelanocortin in lymphocytes in a rat model of inflammatory pain

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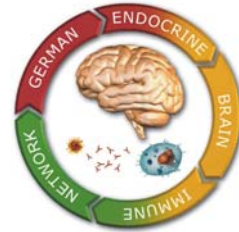
Our previous studies have shown that monocytes/macrophages, granulocytes, and lymphocytes release opioid peptides in the presence of different releasing factors at the site of peripheral tissue injury or inflammation and thereby contribute to opioid-mediated reduction of pain.

We are interested in the regulation of β -endorphin and its precursor proopiomelanocortin (POMC) at the transcriptional and posttranslational level in lymphocytes, as such cells play a role in chronic inflammation. We hypothesized that i) POMC gene expression in the lymph node draining inflamed tissue is up-regulated in inflammation, and ii) that the precursor is cleaved by the prohormone convertases (PC)1 and PC2 similar to neuroendocrine cells in the pituitary gland.

We found elevated POMC gene expression and β -endorphin levels in cells of lymph nodes draining inflamed tissue, as assessed by qPCR and radioimmunoassay. Our PCR and immunocytochemistry data show that PC1 mRNA and protein expression, respectively, are induced after induction of inflammation. PC2 required no stimulation and was detectable using PCR and immunocytochemistry, both, in cells from naïve and activated lymph nodes.

Our findings indicate that β -endorphin synthesis in lymphocytes may depend on the presence of PC1/3, while PC2 alone does not seem to be sufficient. Functional experiments are necessary to verify the specific roles of these enzymes for POMC processing in cells of the immune system.

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Functional stress response in patients with rheumatoid arthritis: Impact of genetic factors

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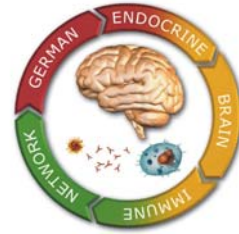
It is still incompletely understood how the stress response contributes to the pathogenesis of rheumatoid arthritis (RA). To characterize neuroimmune interactions, common variants in the genes of the β 2-adrenergic receptor (beta2AR) and corticotropin releasing hormone (CRH) were studied together with functional stress responses in RA patients.

An allele-specific PCR was used to determine the polymorphisms of the beta2AR (position 16, 27, 164), as well as the polymorphic sequences in the 5' flanking region of the human CRH gene in RA patients (n = 310) and controls (n = 305). The autonomic response upon stressful stimuli was investigated studying heart rate variability, and the dynamics of blood glucose levels, CRH, and cortisol production under insulin hypoglycemia (IHT).

There was a highly significant distortion in the distribution of the beta2AR polymorphism at codon 16 between RA patients and controls ($p = 0.00001$). It was also revealed a significant decrease of parasympathetic activity in patients with homozygosity for Gly 16 compared to Arg16Gly RA patients. In addition, the CRH promoter polymorphisms exerted a significant influence on the stress response of RA patients undergoing IHT. The integrated cortisol response to hypoglycemia was significantly lower in RA patients bearing the A1B1 allele compared to the A2B2 ($p = 0.016$).

Polymorphisms of the beta2AR and CRH are associated with disturbed functional stress reactivity on various levels in RA patients. Further studies are warranted to determine the role of genetic factors on stress response in the disease process of RA.

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Collagen-induced arthritis impairs osteoclastogenesis and reactivity to sympathetic neurotransmitter stimuli in bone marrow-derived macrophages from DA rats

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Osteoclasts (OC) are key players in bone destruction in rheumatoid arthritis (RA). Recent work showed that catecholaminergic nerve fibers are reduced in RA synovial tissue. Studies on sweat gland innervation revealed that catecholaminergic fibers are capable of phenotypic transition to cholinergic nerves. The sympathetic neurotransmitters norepinephrine (NE) and acetylcholine (ACh) affect osteoclastogenesis oppositely and that is why we wanted to study osteoclastogenesis at different phases of collagen-induced arthritis (CIA) in an altered neurotransmitter microenvironment.

The influence of NE and ACh on differentiation and activity of bone marrow macrophage (BMM)-derived osteoclasts from arthritic and control animals were compared at various time-points after arthritis induction. The expression profile for adrenergic and ACh receptors was analyzed on mRNA level.

The number of OCs was tendentially lower in arthritic animals. Stimulation with ACh yielded significantly more OCs in controls. NE decreased osteoclastogenesis via β -adrenoceptors and enhanced via α -adrenoceptor stimulation. Cells from arthritic animals were less affected. In form of a trend, osteoclasts from arthritic animals showed decreased activity in cathepsin K activity and in a pit formation assay. The receptor gene expression profile changed in the time course of arthritis. After 20 days past immunization, muscarinic ACh receptors M3 and M5 were significantly upregulated whereas after 40 days adrenoceptors α 1D and α 2B were significantly downregulated.

We conclude that CIA suppresses OC differentiation and activity as well as reactivity to neurotransmitter stimulation but the underlying processes remain to be demonstrated.

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The role of substance P and noradrenaline in callus differentiation

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During the progress of fracture healing, bone and fracture callus become innervated by substance P (SP) and noradrenaline (NA) containing sensory and sympathetic nerve fibers. Aim of this research is to analyze the impact of SP and NA on callus differentiation and biomechanical bone parameters in a murine fracture model and an ex vivo fracture explant model.

We studied unstabilized tibia fractures and stabilized femora fractures in wild type (WT), tachykinin 1-deficient (Tac1^{-/-}) and sympathectomized mice. We further applied callus measurement, biomechanical testing (torque/angle of failure/stiffness), callus explants cultures, and quantitative RT-PCR.

Fracture calli of Tac1^{-/-} mice exhibited a lower volume and a higher physical density compared to WT. Fractured femora of WT mice resisted stronger bending forces compared to Tac1^{-/-} and resisted to greater torque than femora of Tac1^{-/-} and sympathectomized mice. Control legs of WT mice resisted to greater torque and were more stiff compared to Tac1^{-/-} and sympathectomized mice. Biomechanical parameters of newly formed bone after fracture healing were not different to existing bone of control legs. Gene expression of tissue inhibitors of matrix metalloproteinases (timp)-1, -2, -3 and neurokinin-1 receptor were upregulated after stimulation with SP (10⁻⁸ M) and IL-1 β (0.5 ng/ml) and downregulated without IL-1 β (SP 10^{-8/10} M). In callus chondrocytes of Tac1^{-/-} mice, gene expression of *timp-2*, -3, matrix metalloproteinases 3 and 14 (*mmp-3*, -14) and *cox2* is higher than in WT mice.

SP regulates the expression of genes that play a role in matrix composition in the inflammatory phase and alters callus size and density. NA and SP affect the mechanical stability of bone in general but not of newly formed bone after fracture healing.

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Analyzing the microarray mRNA profile of graying human hair follicles: a promising approach in stress and aging research

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Regenerative medicine needs new but safe treatment approaches to balance the reported increase in stress and aging related diseases. Graying is one hallmark of aging and is associated with excessive oxidative as well as psycho-emotional stress. In graying individuals fully pigmented hair follicles are found next to white and intermediary hair follicles. Thus, young and old hair follicles are observed in parallel that share the identical genetic background.

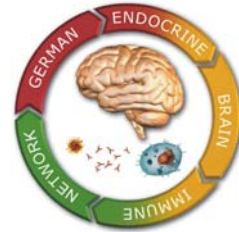
Here, we discuss data obtained by microarray analysis of 15 tissue samples, and we studied the functional relevance in the *ex vivo* hair follicle organ culture model.

We found the expected regulation of genes responsible for pigment-production by melanocytes, the cells that generate the pigment and are gradually lost from graying hair follicles. Among the around 200 regulated genes, we also found genes associated with cellular energy metabolism (e.g. glutaminase) and with nerve fiber growth (e.g. plexin C1). These results could be confirmed on mRNA and protein level as well as by pathway-analysis. *Ex vivo* treatment of cultured hair follicles with L-glutamine or plexin C1 revealed biological relevance and pharmaco-interventional potential of these selected microarray-results in that these compounds were able to halt the culture-induced premature aging process and cellular stress responses (pigment production, cell proliferation, -differentiation, -apoptosis, senescence).

We therefore consider the graying hair follicle a useful model to study aging and stress associated responses and report here energy metabolism and cellular plasticity as important areas for future research.

*néé Gräub

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Neuroendocrine mediators regulate production of B cell activating factor of the tumor necrosis factor family (BAFF) in human synovial fibroblasts

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B cell activating factor of the tumor necrosis factor family (abbreviated BAFF) is a cytokine important for the stimulation and survival of autoreactive B cells and, therefore, might play a role in several autoimmune disease, e.g. autoimmune arthritis. In psoriasis arthritis (PsA), BAFF correlates with disease activity and testosterone, but only in male patients, suggesting a role for sex hormones in the regulation of BAFF. Thus, we wanted to determine whether BAFF production is regulated by neuroendocrine mediators in rheumatoid arthritis (RA) and osteoarthritis (OA) synovial fibroblasts.

First, fibroblasts isolated from synovial tissue of RA (n=10) and OA (n=10) patients were cultured in the presence or absence of interferon (IFN)- γ , IL-1, lipopolysaccharide (LPS), tumor necrosis factor (TNF) and cortisol in different combinations for 24, 48, and 72 hours to determine the optimal stimulation strategy for induction of BAFF production (measured by ELISA in supernatants).

IFN- γ in a concentration-dependent manner induced BAFF in RA and OA fibroblasts. Interestingly, we were able to induce significantly more BAFF in synovial fibroblasts from OA patients as compared to RA patients. Additionally, IFN- γ induced BAFF production in fibroblasts (OA n=10, RA n=10) was decreased by α -adrenergic and increased by β -adrenergic mechanisms. Furthermore, estradiol inhibited and dihydrotestosterone increased IFN- γ production.

Taken together, BAFF production in synovial fibroblasts is modulated by sex hormones and adrenergic stimuli. Therefore, the known influence of neuroendocrine mechanisms in the context of arthritis might be in part mediated by regulating BAFF production from synovial fibroblasts via regulation of IFN- γ .

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Neural noradrenergic control of experimental Chagas' disease

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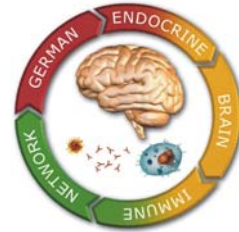
It is well established that immune-noradrenergic reflexes and modulatory effects exerted by sympathetic nerves occur during inflammatory and immune responses. Here we studied the operation of the sympathetic nervous system (SNS) in mice infected with the intracellular parasite *Trypanosoma cruzi* (TC), the causal agent of Chagas's disease, a pathology that affects millions of individuals in South and Central America.

C57Bl/6J mice were infected with 100 parasites, and survival, noradrenaline (NA) content in the spleen, parasite load, and cytokines, antibodies against TC, and corticosterone blood levels were evaluated.

Hundred percent lethality in males and survival of a considerable proportion of females paralleled by a reduced cytokine response, indicated a sexual dimorphism during this infection. Corticosterone blood levels were increased in mice of both sexes but were more elevated in females. There was a clear reduction in the NA content of the spleen and in the number of tyrosine hydroxylase-positive nerve fibers, an effect that was more pronounced in males than in females. To analyze the relevance of these alterations for the course of the disease, animals were chemically sympathetically denervated prior to the inoculation of the parasite. Sympathetic denervation resulted in increased parasitemia, early death of males, a significant increased lethality in females, and increased levels of IL-6, IFN γ , and IL-10, without changes in antibody levels.

These studies provide further evidence for the neural control of immune and infective processes, in this case, during a parasitic infection.

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A feedback loop involving microRNA regulates opioid- and cannabinoid-functions

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Mu opioid receptors (MOR) mediate the effects of most of the clinically used opioids including morphine and methadone. Likewise, type 1 (CB1) and type 2 cannabinoid receptors mediate many effects of cannabinoids.

Here, we report that MOR and CB1 are regulated by microRNA in human neuroblastoma SH SY5Y cells and in human Jurkat T lymphocytes: Using overexpression and inhibition of distinct microRNA species, we demonstrated that MOR are regulated by let7A, let7D and mir98, while CB1 were regulated by 23B and let7D. MicroRNA are key regulators of eukaryotic gene expression. By binding to complementary homologous mRNA sequences they inhibit their translation. The endoribonuclease dicer is a key enzyme in the maturation of microRNA. Interestingly, we also found that agonists of both, MOR and CB1 induce the expression of dicer in our cell models, thereby upregulating microRNA: Western blot experiments revealed a significant upregulation of dicer in cells stimulated with morphine or metanandamide for four to eight days. Using reporter gene analysis, we demonstrate upregulation of functional microRNA by morphine and metanandamide.

In conclusion, by this regulatory loop, the activity of the opioid and cannabinoid systems in the brain are regulated, which may explain in part phenomena such as tolerance and addiction. In addition, since many immune cell functions are regulated by microRNA, this may explain a number of the immunomodulatory effects of these drugs, e. g. their effect to induce a T helper cell type 2-skewed immune response, which is known to depend on dicer.

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The peripheral nervous system and focal bony erosions in arthritis

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Sympathetic and sensory nerve fibers innervate bone and joint adjacent tissue. Apart from transmitting signals to the brain (afferent function), they also play an important role in bone homeostasis (efferent function). Under certain conditions sympathetic nerve fibers are able to change their phenotype from noradrenergic to cholinergic. Anti-inflammatory effects mediated by the $\alpha 7$ subunit-containing nicotinic acetylcholine receptor have been described (work of Tracey's group). We asked whether this transition might occur near focal erosions during collagen-induced arthritis (CIA) in mice or in co-culture experiments of murine sympathetic ganglia and osteoclast progenitor cells.

Limbs from 30 immunized C57Bl/6J mice were collected at distinct time points covering all stages of the disease. Sections of limbs from CIA experiments as well as sympathetic ganglia from co-culture experiments were stained for tyrosine hydroxylase (TH), the key enzyme for catecholamine synthesis (noradrenergic fibers), and vesicular acetylcholine transporter (VACHT, cholinergic fibers) by immunofluorescence.

In mouse joint sections, an increase in the ratio of cholinergic to adrenergic nerve fiber density at day 35 after immunization was observed. However, most of the nerve fibers were located in joint adjacent skin or muscle tissue, only few in synovium or directly in the erosion. Co-culture experiments of sympathetic ganglia and osteoclast progenitors obtained from healthy mice showed increased cholinergic activity as compared to experiments with cells from mice with CIA.

Taken together, these results suggest that cholinergic innervation in the joint region is upregulated under inflammatory conditions and that catecholaminergic nerve fibers are influenced by osteoclast progenitor cells.

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Inadequate glucocorticoid secretion in experimental arthritis in rats is closely linked to impaired mitochondria and reduced lipid breakdown in the adrenal cortex

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In rheumatoid arthritis a functional deterioration of the HPA-axis in form of inadequately low secretion of glucocorticoids in relation to severity of inflammation can be detected. The reasons for this phenomenon are not known. The purpose of this study was to find possible reasons responsible for adrenal insufficiency during arthritis.

DA rats were immunized with type II collagen in incomplete Freund adjuvant to induce arthritis. Plasma corticosterone was evaluated by RIA and plasma ACTH and IL-1 β by ELISA. Adrenal cholesterol was quantitatively studied by Sudan-III staining and scavenger receptor class BI (SR-BI, the HDL receptor) by immunohistochemistry. Fluorescent NBD-cholesterol uptake kinetics were analyzed by flow cytometry. Ultrastructural morphology of adrenocortical mitochondria and lipid droplets was studied by electron microscopy.

Initially increased corticosterone and ACTH levels were reduced to baseline levels in the later phase of the disease. Serum levels of corticosterone relative to IL-1 β were markedly lower in arthritic than control animals (inadequacy). Cholesterol storage in adrenocortical cells and expression of SR-BI did not differ between immunized and control rats. However, number of impaired mitochondria largely increased during the course of arthritis (maximum on day 55), and this was paralleled by reduced numbers of activated cholesterol droplets (inhomogeneous droplets relevant for generation of glucocorticoids). In addition, number of normal mitochondria positively correlated with serum corticosterone levels.

This first study on adrenal reasons for inadequate glucocorticoid secretion in arthritis demonstrated impaired mitochondria and altered cholesterol breakdown paralleled by low corticosterone levels in relation to ongoing inflammation.

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Neuroendocrinology and Immune Function

The role of estrogen and ER α/β in the sensory and sympathetic nerve fibre imbalance in peritoneal endometriotic lesions

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Endometriosis is a chronic-inflammatory disease, which is characterized by the presence of endometrial-like tissue outside the uterine cavity (prevalence: 15-20%). Recently, we were able to detect an imbalance between sensory and sympathetic nerve fibers (NF) in peritoneal endometriotic lesions (pEL), with a hyperinnervation of proinflammatory sensory NF, and a hypoinnervation of anti-inflammatory sympathetic NF and corresponding neurotransmitters. Many painful conditions occur more frequently in women. Estrogens have neuromodulatory effects on the nervous system. For example, as in rodents, the density of myometrial-sympathetic NF decrease during the estrogen-dominant phases of the cycle.

In this study, we investigated the role of estrogen on the disturbed innervation in pEL. In addition, the 17 β -estradiol (E2) concentration in 100 samples of peritoneal fluid (PF) of patients with endometriosis was compared to controls (n=50), and PF was used to study behavior of sensory and sympathetic nerve fibers in outgrowth assays.

This revealed a higher E2 concentration in endometriotic patients compared to controls (p<.001). Aromatase is overexpressed in pEL. Immuno-double-stained pEL (n=15) prove that ER α/β are co-localized with endometriosis-associated NF. With the neuronal-growth-assay (chicken-embryonic sensory and sympathetic ganglia), we were able to show an estrogen-induced neurite-outgrowth in sensory ganglia, whereas, increasing estrogen-concentrations reduced the sympathetic-outgrowth (p<0.05). PF of patients with endometriosis induced an elevated sensory and a reduced sympathetic sprouting compared to the control (p<0.001), and they expresses higher levels of ER α but lower ER β (mRNA and Protein) (p<0.001).

In conclusion, as E2 induced neurite outgrowth from sensory ganglia and reduced neurite sprouting from sympathetic ganglia, and since E2 was elevated in PF of patients with endometriosis, and both ER α/β were expressed on endometriosis-associated nerve fibers, we suggest that the NF imbalance in endometriosis is estrogen-dependent. This phenomenon might explain the proinflammatory painful condition in endometriosis driven by high levels of estrogens.

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Higher basal interleukin-6 and cortisone levels in poor sleeping pregnant women but not in poor sleeping young mothers

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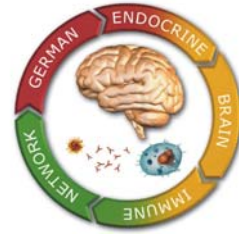
Pregnancy and postpartum period are characterized by distinct changes in sleep including increased sleep fragmentation and decreased sleep efficiency. Sleep changes can persist up to several months postpartum. Therefore, a considerable fraction of pregnant women (PW) as well as young mothers (YM) can be considered as chronically partial sleep-deprived. Partial sleep deprivation is known to detrimentally affect, e.g., stress axes, immune system, and well-being. The present study aimed to investigate consequences of partial sleep deprivation in PW and YM concerning those systems.

In total, 166 PW and 154 YM participated in the study. According to their sleep efficiency objectively measured via actigraphy over 7 consecutive nights, we divided PW as well as YM in a group of poor and well sleeping individuals. We obtained a fasting blood sample in order to quantify basal levels of interleukin- (IL-) 6. Cumulative long-term cortisone levels were analyzed in hair and well-being was estimated via questionnaires.

Sleep of poor sleeping PW and YM was characterized by decreased sleep efficiency and increased sleep fragmentation compared to well sleeping women. We found significant higher basal IL-6 concentrations, cortisone levels, and depression scores in poor sleeping PW (all p-values below 0.041) but not in poor sleeping YM.

Data provide evidence that poor sleeping PW, but not YM, are negatively affected by partial sleep deprivation. Altered hormonal status in pregnancy, physiological habituation to partial sleep deprivation over time postpartum, or compensating mechanism through pleasure about the child might explain diverse results in both groups.

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Synovial fibroblasts are novel target cells for the melanocortin peptide α -melanocyte-stimulating hormone

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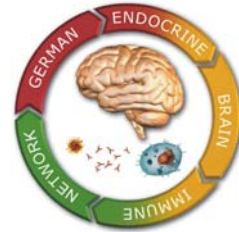
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There is increasing evidence that the proopiomelanocortin (POMC) system plays an important role in the osteoarticular system (Böhm & Grässel, *Endocr. Rev.* 2012). However, whether synovial fibroblasts express receptors for α -melanocyte-stimulating hormone (α -MSH) and/or generate proopiomelanocortin (POMC)-derived peptides is unknown.

We show that synovial fibroblasts from OA patients express melanocortin-1 receptor (MC1R) on the RNA and protein level *in vitro*. MC1R immunoreactivity is also detectable in fibroblasts of synovial tissue *in situ* as shown by immunofluorescence analysis. The detected MC1R in synovial fibroblasts is weakly coupled to adenylate cyclase as demonstrated by increased intracellular cAMP but not Ca^{2+} levels after α -MSH treatment. Notably, α -MSH significantly reduced IL-1 β -mediated secretion of IL-8 in half of the donors (n=6) while in the others it had no effect. Furthermore, although truncated POMC transcripts are present in cultured synovial fibroblasts from OA patients, these cells neither expressed full-length POMC mRNA, POMC protein, nor secreted detectable α -MSH amounts into the culture media, ruling out an autocrine loop for melanocortin peptides.

Our findings highlight synovial fibroblasts as a novel target cell type for melanocortins within the osteoarticular system and encourage further exploitation of such peptides for the treatment of inflammatory and/or degenerative joint diseases.

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A new role of the oxytocin system in human skin stress responses and implications for atopic dermatitis

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and Gitta Neufang^a

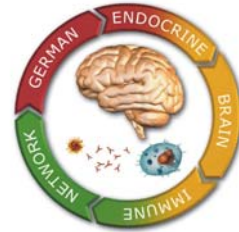
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The neuropeptide hormone oxytocin (OXT) mediates a wide spectrum of tissue-specific actions, ranging from cell growth, cell differentiation, sodium excretion to stress responses, reproduction and complex social behaviors. OXT is known to modulate neuroendocrine stress responses, inflammatory processes and to counteract the hypothalamus-pituitary-adrenal axis. Recently, OXT expression has been detected in keratinocytes, but its function is still unexplored in human skin.

Here, we show that both, OXT and its receptor, are expressed in primary human skin cells. OXT induces dose-dependent calcium-fluxes in dermal fibroblasts and keratinocytes, indicating that the OXT receptor (OXTR) is functionally expressed in both cell types. In order to investigate potential OXT-mediated functions in skin stress responses, we performed OXTR-knockdown experiments. OXTR-knockdown in dermal fibroblasts and keratinocytes lead to elevated levels of reactive oxygen species and reduced levels of glutathione. In keratinocytes, an increased release of proinflammatory cytokines, such as IL-6, RANTES, and CXCL10 was observed.

In conclusion, atopic dermatitis, a multifactorial inflammatory skin disease, is characterized, among others, by an increased susceptibility to oxidative stress. We detected a reduced expression of the OXT system in lesional and peri-lesional atopic skin suggesting a clinical relevance in skin homeostasis.

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The chondroprotective role of the melanocortin system in murine osteoarthritis

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Originally defined as neurohormones, melanocortins (MCs) exhibit a wide spectrum of physiological effects. An increased level of α -MSH was detected in osteoarthritic synovial fluid. In addition, we recently demonstrated that melanocortin-1 receptor (MC-1R) is expressed in human chondrocytes. In the presence of MC-1R, α -MSH shows anti-inflammatory and cytoprotective effects in many different cell types. Based on these findings, we suggest a chondroprotective role of α -MSH and its receptor MC-1R in cartilage physiology.

To identify the role of MC-1R-signaling in osteoarthritis (OA), a surgically induced OA model was applied in MC-1R signaling-deficient mice (MC-1R^{e/e}): the destabilization of the knee joint by incision of the medial meniscotibial ligament (DMM). After 2, 4, 6, 8 and 12 weeks post surgery, knee joints were prepared for histological evaluation of articular cartilage and subchondral bone plate by sectioning and safranin O/fast green staining. Subchondral bone structure was analyzed with *in vivo* μ CT.

After 4 and 8 weeks following surgery, the area of degenerated articular cartilage in MC-1R^{e/e} was significantly increased compared to wildtype (WT). Morphometric and *in vivo* μ CT analysis demonstrated alteration in subchondral bone structure in MC-1R^{e/e} compared to WT mice.

Our data suggest that degeneration of articular cartilage in MC-1R^{e/e} mice progresses faster than in WT, which points towards a more severe OA-progression. Hence, the melanocortin system could play a chondroprotective role in development of early OA.

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Alterations in diurnal cortisol secretion, cognitive performance and frailty in an aging population: preliminary results of the KORA Age 1 Study

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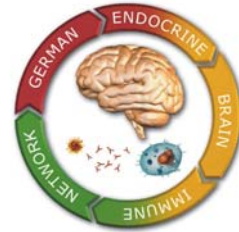
Dysregulated cortisol secretion is hypothesized to be etiological in the development of heart disease, osteoporosis, cognitive decline and frailty in the elderly. However, the variance of cortisol regulation has not been assessed within this context. We sought to examine associations between variances of diurnal salivary cortisol measurements and cognitive performance / frailty in healthy elderly people.

A cross-sectional analysis was conducted using data obtained from the KORA Age population-based study. Salivary cortisol samples were collected from participants using Salivette® collection devices at awakening, 30 minutes after awakening, and late evening. Cognitive performance was assessed by the Telephone Instrument for Cognitive Status (TICS) adjusted for education per Lacruz et al. 2012, and frailty was defined according to Fried et al. 2001.

Among 744 (377 male and 367 female) study participants, 4.4% (N=33) suffered from probable dementia, and 15.3% (N=114) had mild cognitive impairment. Significant differences were observed between cognitive status and cortisol measures in the morning (p-value 0.021), 30 minutes after awakening (p-value 0.002), and in the ratio of morning versus late evening cortisol levels (p-value 0.019). A small portion of participants were classified as frail (3.36%, N=25), yet over a third (35.2%, N=262) were pre-frail. Cortisol measures of 30 minutes after awakening (p-value 0.019), late evening (p-value 0.003) and the ratio of morning versus late evening cortisol levels (p-value 0.0002) showed significant associations with these distributions. No significant associations were observed with the commonly used cortisol awakening response.

Associations between salivary cortisol and cognitive performance or frailty were strongest when considering the ratio between morning and evening levels of cortisol. Future investigations will apply analytical models to further understand cortisol homeostasis particularly in the context of cognition and frailty in people with advanced age.

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Effects of mifepristone on T cell subsets in humans

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In humans, blood T cell numbers are highest at 2 AM and lowest at 11 PM. This rhythm mainly reflects changes in numbers of CD4 and CD8 naïve (TN) and central memory T cells (TCM) that are reduced due to rising cortisol levels in the morning. Preliminary data indicate that cortisol induces an upregulation of CXCR4 on TN and TCM and, thereby, redirection of these cells to the bone marrow. To elucidate whether this effect is mediated by the glucocorticoid receptor (GR) we administered the GR antagonist mifepristone (MIF, 200 mg) in a randomized placebo controlled study at 11 PM to 16 healthy young men and monitored T cell subsets until 9:30 AM. In the placebo condition, cortisol and CXCR4 increased in the morning while TN and TCM counts showed a concomitant decline. Unexpectedly, MIF failed to prevent these morning changes in CXCR4 and T cell numbers, presumably, due to enhanced cortisol levels. At night, MIF even showed partial agonistic actions with increases in CXCR4.

In a second experiment we took blood from 13 healthy young men at night and in the morning and measured CXCR4 expression on T cell subsets after culturing cells in the presence or absence of MIF. Again, MIF increased CXCR4 on TN and TCM at night. In contrast, MIF clearly suppressed CXCR4 on these T cell subpopulations in the morning. The latter finding corroborates the assumption that systemic increases in cortisol counteracted the GR antagonistic effects of MIF on CXCR4 in the in vivo experiment.

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Immunomodulation of angiogenic factor production in pituitary tumor cells under basal and hypoxia mimicking conditions.

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In pituitary adenomas, which are known to display decreased vascular density in comparison to normal pituitary tissue, the exact role of angiogenesis in tumor transformation and progression remains unclear. As recent studies have shown that patients with pituitary adenomas display elevated inflammatory markers such as IL-8 and TNF- α , we have conducted initial investigations to further clarify the possibility of inflammation-induced angiogenesis in pituitary adenomas.

To further explore these mechanisms, the murine folliculo-stellate-like TtT/GF cell line and human pituitary adenoma primary cell cultures were treated with the TLR-4 ligand LPS under basal and hypoxia-mimicking conditions (CoCl₂ treatment). HIF-1 α and NF- κ B expression was then studied by Western Immunoblotting. VEGF-A and IL-8/KC were measured by ELISA. Additional CD-31 immunohistochemistry of vessel density was performed. Finally, RT-PCR was conducted to verify the presence of TLR-4 and IL-8 receptors in human tumors.

We observed that both LPS and CoCl₂ treatment strongly induce HIF-1 α and NF- κ B protein expression as well as VEGF-A and IL-8/KC secretion in all cell populations studied, suggesting possible crosstalk mechanisms. An interesting dichotomy of the angiogenic response (VEGF-A and IL-8 production) within tumor subtypes following LPS stimulation was observed, suggesting possible tumor-specific mechanisms of inflammatory responses.

These results suggest that inflammation may play a role in angiogenesis in pituitary tumors. This not only provides the basis for further investigation of inflammation-induced angiogenesis, but also provides insight into the mechanisms of angiogenesis in pituitary adenomas in general, which when further understood may provide improved options for treatment and prevention.

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Influence of *CYB5A* gene variants on risk of rheumatoid arthritis and local endocrine function in the joint

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Rheumatoid arthritis (RA) is a multifactorial disease with a complex genetic background. An autoimmune etiology is involved in RA onset and progression but other pathways like neuroendocrine effects are potentially important.

Androgens such as dehydroepiandrosterone, androstenedione and testosterone act anti-inflammatory. Endogenous *de novo* synthesis of androgens depends mainly on two enzyme activities of cytochrome P450c17: 17- α -hydroxylase and 17,20 lyase. A co-factor, particularly for 17,20-lyase activity, is cytochrome b5 (type A), encoded by the *CYB5A* gene on chromosome 18. We hypothesized that gene variants in *CYB5A* trigger the local amount of hormones, especially androgens and side products in this pathway, in the joint and therefore affect the susceptibility to RA.

We screened two available genome wide association study (GWAS) data sets for association between single nucleotide polymorphisms (SNPs) in or near the *CYB5A* gene and RA. Both GWAS revealed RA-associated polymorphisms in the *CYB5A* gene: rs1790834 ($p=0.0073$, OR=0.83) and rs1790858 ($p=0.0095$, OR=0.44), respectively. We sought to replicate these findings in our Slovak RA sample with $n=521$ RA cases and $n=321$ healthy controls. For rs1790834 localized in intron 1 of the *CYB5A* gene, association was found with an OR=0.69, i. e., a protective effect of the rare allele ($p=0.008$). Genotype dependent gene expression in synovial fibroblasts, a cell type potentially responsible for androgen biosynthesis in the joint, showed an association between the rare allele of rs1790834 and increased *CYB5A* expression ($p<0.0005$). Immunohistochemistry with a specific anti-cytochrome b5 antibody confirmed the mRNA expression data in synovial tissue.

In conclusion, this study demonstrates for the first time that cofactors of important androgen-generating enzymes such as cytochrome b5A plays an important role for RA susceptibility. The interaction with neuroendocrine factors will be discussed.

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Stress, Behavior and Immune Function

Biological and psychological predictors of visceral pain sensitivity in healthy women

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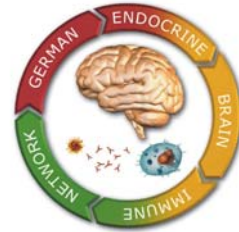
Whereas psychological, immunological and HPA-axis related factors have been implicated in pain sensitivity in several pain models, insight into the mechanisms of visceral pain sensitivity is still limited. The current study aimed to investigate psychological and biological predictors of visceral pain sensitivity in healthy subjects.

In N= 59 healthy females, measures of gastrointestinal (GI) symptoms in daily life, trait and state anxiety, depression, serum cortisol, and serum levels of interleukin (IL)-6 were obtained, followed by assessment of rectal distension pain sensitivity measures (i.e. rectal distension sensory threshold, pain threshold, and pain ratings for discrete rectal distension stimuli at pain threshold level).

Regression analyses revealed that more GI symptoms in daily life predicted lower sensory thresholds. Further, lower pain thresholds were predicted by increased GI symptoms, higher state anxiety and cortisol concentrations, whereas increased cortisol was also associated with lower pain ratings. IL-6 was positively related to GI symptoms and negatively to the pain threshold, but was a non-significant predictor of pain thresholds in the multiple regression analysis.

Similar to findings in patients with functional GI symptoms, we showed that subclinical GI symptoms predict visceral pain sensitivity. In line with somatic pain findings, state but not trait anxiety was found to predict visceral pain sensitivity. Our findings on serum cortisol as predictor point to a differential effect of cortisol on the different aspects of pain sensitivity. Our finding on the role of IL-6 in GI symptoms and pain sensitivity is promising for understanding gastrointestinal complaints in patients and needs further investigation.

Please find the abstracts via URL: <http://dx.doi.org/10.1016/j.bbi.2013.01.074>



Does repeated anticipation induce neuroendocrine modulation of the immune system in domestic pigs?

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To improve animal welfare in pig husbandry it is necessary to expand our knowledge of affective states and their physiological effects. In our study, we used a controlled setup to induce affective states and neuroendocrine immune modulation. For each trial, six female piglets were being housed in individual pens in the same room. Three of these piglets were conditioned six times a day to a sound that was followed by a positive stimulus (food), a negative stimulus (air-puff) or a random choice of food or air-puff. This was supposed to induce positive, negative or conflicting anticipation, respectively. The other three piglets obtained positive, negative or no stimuli without conditioning and served as controls. Within four weeks, we expected changes in mood and consequently physiological effects. Preliminary analyses showed an increase in heart rate and heart rate variability in positively anticipating pigs during the sound reflecting an activation of the sympathetic nervous system. These animals also showed an increased serotonin turnover in the ventral tegmental area and a significant decrease in SEB-induced T-cell proliferation. The immunoglobulin production showed an age-dependent increase which was less pronounced for IgM of positively anticipating pigs. While plasma ACTH and salivary cortisol concentrations decreased during the experiment indicating adaptation, there were no treatment-induced effects and in line with this no differences in CRH and GR gene expression in the brain.

Our data indicate that a supposedly positive anticipation may be accompanied by a frequent arousal of the pigs with a potentially negative influence on immunocompetence.

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Adoptive transfer of CD4⁺ mesenteric lymph node cells from mice exposed to chronic psychosocial stress: physiological and immunological consequences

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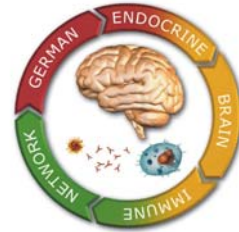
Chronic subordinate colony housing (CSC) is an adequate mouse model of chronic psychosocial stress, besides other behavioural and physiological consequences inducing development of spontaneous colitis. The latter is characterized by an increased histological damage score and activation of T cells in the draining mesenteric lymph nodes (mesLN).

Here, we isolated total mesLN cells (mesLNC) from CSC and single housed control (SHC) mice, separated CD4⁺ mesLNC, quantified their anti-CD3-stimulated interferon- γ (IFN- γ) secretion, and adoptively transferred 3×10^6 of these cells into naïve syngenic C57BL/6 male recipient mice. One week later, recipient mice were killed and selected physiological and immunological parameters assessed.

While the number of mesLNC was more than three-fold increased following CSC, the percentage of CD4⁺ cells was strongly decreased in CSC (14.5 %) compared with SHC (27.3 %) donor mice. However, CD4⁺ mesLNC of CSC compared with SHC donor mice produced significantly more IFN- γ . Furthermore, CSC recipient mice showed increased absolute spleen and adrenal weights, plasma corticosterone concentrations, numbers of total mesLNC, and IFN- γ secretion from these cells during anti-CD3 stimulation.

Currently, we are assessing the cellular composition of mesLNC in CSC and SHC donor mice by flow cytometry and the colitogenic potential of adoptively transferred CSC and SHC CD4⁺ mesLNC in RAG-1-deficient mice, respectively. Together, our results indicate that transfer of a single cell population from chronic psychosocially-stressed mice induces an overall pro-inflammatory milieu in naïve recipient mice, probably contributing to an overall risk for developing inflammatory disorders, i.e. colitis.

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Influence of housing on endocrine function and immune system in pregnant sows

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Regrouping of unfamiliar animals as well as individual housing can lead to social stress causing an activation of physiological stress systems that affect various immune functions. Whereas EU guidelines (2001/88/EG) impose the housing of pregnant sows in social groups by 2013, individual housing is still the most conventional housing system in numerous countries. However, the effects of different housing systems on immune functions in pregnant sows are poorly investigated. Therefore, this study aimed at characterizing endocrine and immunological responses during the second half of gestation in sows kept in different housing systems

Blood samples of pregnant sows (German Landrace) either housed in single crates ($n = 11$) or in a dynamic group ($n = 22$) were taken 7, 6, 4, and 2 weeks pre partum and the number of different leucocyte subpopulations, the proliferative response of lymphocytes to stimulation with concanavalin A or pokeweed mitogen as well as plasma cortisol concentrations were evaluated.

Significantly higher absolute numbers of helper T cells ($CD3^+CD4^+CD8^{+/-}$) as well as cytotoxic T cells ($CD3^+CD4^-CD8^+$) were found in group housed sows at most sampling points. Proliferative lymphocyte responses to each mitogen did not differ between sows of the two housing systems. However, sows kept in single crates showed a tendency for higher cortisol concentrations 7 weeks pre partum and significantly higher cortisol concentrations two weeks before parturition.

In summary, these results indicate substantial effects on the neuroendocrine-immune system of pregnant sows depending on the housing system, which might affect their ability to deal with infection.

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Maternal prenatal life events increase risk for atopic disorders in children

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Prenatal stress exposure may affect maternal immune adaptation to pregnancy and fetal immune development, predisposing the child to atopic diseases. Significant levels of prenatal maternal anxiety and/or exposure to bereavement during pregnancy have been associated with the development of atopic diseases in offspring, yet insights on the effect of multiple, common prenatal stressors are rare. Moreover, it is also unclear if prenatal stress challenge modifies the risk for atopic diseases in the context of parental atopy.

We tested whether women's experiences of negative prenatal life events during the first or second half of pregnancy predicted the risk of developing atopic disorders in their children, and whether parental atopy moderated this association.

Using multivariable logistic regression we calculated the odds of a child having asthma, eczema and/or allergic rhinitis at ages 6 or 14 years associated with maternal prenatal exposure to negative life events in a sample of 1587 children from the Western Australian Pregnancy Cohort (Raine) Study. After adjusting for confounding variables, the likelihood of asthma, allergic rhinitis or eczema at age 14 was significantly increased in the children of mothers who had experienced negative life events during the second half of gestation, suggesting a critical period of fetal immune development. The association between prenatal stress and increased risk for asthma was stronger in children of non-asthmatic compared to asthmatic mothers.

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Stress related modulation of glucocorticoid sensitivity and T cell responses in human pregnancy

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A tailored T cell response to pregnancy plays a key role in maintaining tolerance towards the fetus which can be compared to an “allograft” due to the expression of paternal antigens. High maternal stress perception can interfere with this T cell response which can be mediated by Glucocorticoids (GC). This mediation is dependent on GC sensitivity of T cells controlling T cell proliferation. Our objective was to examine if higher stress perception affects GC sensitivity in T cells and thereby altering pregnancy outcome.

Stress levels of 80 pregnant women were assessed employing the Perceived Stress Scale (PSS). 7 women with high and low stress levels were selected for detection of GC sensitivity of T cell proliferation. T cell phenotypes and frequencies were investigated by flow cytometry. Fetal birth weight served as parameter to evaluate pregnancy outcome. Statistical analyses included T- and Mann-Whitney U-tests. Significance levels were set at a p-value of 0.05.

As expected, women with high and low perceived stress showed a significant difference in stress scores in first ($p < 0.01$) trimester which carried over into the second ($p < 0.05$) trimester. In stressed women, significantly reduced GC sensitivity resulted in higher T cell proliferation and frequencies of CD4⁺ and regulatory T (Treg) cells increased. Interestingly, a significantly higher variance in Treg cells was observed. High levels of stress were associated with reduced fetal weight.

We propose that reduced fetal outcome may result from increased T cell proliferation due to stress-mediated decreased GC sensitivity whereas increasing Treg cells could be an attempt of counterregulation.

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Changes in the systemic immune status following chronic psycho-social stress exposure in male mice

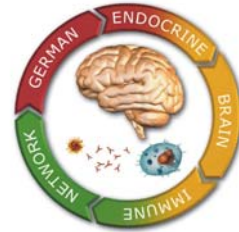
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Animal models of chronic social stress are known to contribute to a great extent to the research of stress-related disorders in humans. Our previous data revealed a generalized activation of T cells and an altered reaction of T cell subtypes not showing a shift towards Th2 responses after 19 days of chronic subordinate colony housing (CSC), a chronic psycho-social stress model in male mice. In this study, we evaluated the time-dependent effects of CSC on the T cell activation status. Our results demonstrated changes in T cell composition concerning CD3, CD8, CD4 as well as Treg, Th1, and Th17 cells. In addition, the activation status of T cells differed during the time of CSC. In conclusion, CSC stress induced distinct changes in the T cell compartment depending on the duration of stress exposure.

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Mediation of the extinction process in behaviorally conditioned immunosuppression

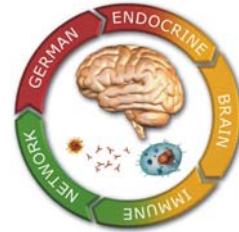
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To analyze neuro-immune-communication, our research group established a model of conditioned immunosuppression in rats which follows the principle of classical (Pavlovian) conditioning. We employed a conditioned taste aversion (CTA) paradigm where the novel taste saccharin (conditioned stimulus/CS) is paired with the immunosuppressive drug cyclosporine A (unconditioned stimulus/US). Upon re-exposure to the conditioned stimulus animals show a reduced CTA (saccharine intake), as well as a significant inhibition of T lymphocyte proliferation and IFN- γ and IL-2 in anti-CD3 stimulated splenic T cells.

Repeated, unreinforced re-exposure to the CS leads to an extinction of the conditioned behavioral (CTA) and immune responses (cytokine inhibition, lymphocyte proliferation). In order to analyze the neurobiological mechanisms responsible for the extinction process we administered the protein synthesis inhibitor Anisomycin, or the beta-adrenergic receptor blocker Propranolol into the insular cortex during evocation, as the insular cortex is known to mediate the learned immune response during re-exposure of the CS. Our preliminary data show a prolonged extinction of the CTA reflected by a reduced CS intake after micro injection of protein synthesis inhibitor Anisomycin but not after administration of Propranolol into the insular cortex. Ongoing experiments will reveal whether the prolonged extinction on the behavioral level can also be detected in the conditioned immune response.

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Is TH17 immunity altered by chronically perceived stress?

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Inflammatory injury requires tissue regeneration, a process hampered by chronic stress exposure in many experimental settings. The reported shift of the immune balance towards adaptive humoral immunity reported in chronically stressed mice and man may be the functional link. We here report results obtained in females exposed to exam stress. In these individuals subjective perception of anxiety (state and trait anxiety index - STAI) as well as a nervous mood (multidimensional mood questionnaire - MDMQ) prominently characterized chronic stress perception throughout a twelve week examination preparation and execution period. During the same time period exam participants displayed reduced morning serum cortisol levels prior to exam (exam preparation) and during exam execution when compared to expression levels in participants not exposed to exam stress. They also showed significantly increased serum level of the neurotrophin brain derived neurotrophic factor (BDNF). Correspondingly, the summary score for cytokines conducting the TH17 response differed significantly between exam participants and controls during exam preparation. These results link decreased hypothalamus pituitary adrenal axis function during chronic stress exposure with increased neurotrophin expression and TH17 dominated immunity. Future research will determine relevance for chronic inflammatory diseases driven by respective immune-dysfunction.

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Stress-induced Local Inflammation Correlates with an Increase in Inflammatory Myeloid Cells

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The correlation between chronic stress and aggravation of inflammatory diseases has long been implied. A variety of studies in men and mice have proven the increase in myeloid cell blood counts as a hallmark of stressor exposure. Redistribution of myeloid cells from primary and secondary lymphoid organs into the blood is thought to be the major reason for that phenomenon. Recently, we established a model of chronic subordinate colony housing (CSC) in male mice. CSC induced an aggravation of DSS-induced colitis. Gut inflammation was accompanied with an increased translocation of commensal bacteria from the gut lumen into the surrounding tissue.

We now analysed changes in the composition and function of myeloid cell subtypes in spleen and gut. CSC stress induced an increase in myeloid cells in blood, spleen and gut. A detailed analysis revealed that CD11b⁺ cells in the spleen consisted mainly of Ly6G⁺ granulocytic cells. Furthermore, myeloid cells from the spleen reacted with an increased cytokine production to in vitro restimulation with LPS indicating an inflammatory phenotype of those cells. CSC also induced up-regulation of CXCL1 and CXCL2 in the spleen and in the gut.

Our study showed a stress-induced accumulation of distinct myeloid cells in secondary lymphoid organs and peripheral tissue that seemed to be mediated by specific chemokines induced during exposure to CSC. Due to their inflammatory phenotype these cells might contribute to the aggravation of local gut inflammation seen in the DSS-induced colitis.

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Placebo responses in patients with house dust mite allergy

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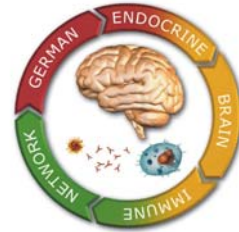
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Peripheral immune responses can be modified by behavioral conditioning. It has also been shown that the anti-allergic effects of the antihistamine desloratadine can be induced after one re-exposition to a conditioned stimulus. However, it is unknown to what extent effects of patients' expectation contribute to this effect and whether the effect can be re-produced over time.

In our study, patients with house dust mite allergy were randomly allocated to a conditioned group (n = 25), a sham-conditioned group (n = 25) or a natural history group (n = 12). Patients in the conditioned group received desloratadine (unconditioned stimulus) together with a novel tasting green drink (conditioned stimulus) on five consecutive days and were re-exposed to the drink together with placebo capsules on five days after drug wash-out. Sham-conditioned patients received the green drink together with placebo capsules throughout the study, whereas natural history patients did not receive any stimuli. To analyze the (learned) placebo response, the allergic reaction was measured after the first and, to assess the reproducibility of the effect, after the fifth evocation through skin prick test and nasal provocation test.

Both conditioned and sham-conditioned patients showed significantly decreased symptom scores after the first as well as after the fifth evocation, indicating that the effect is not restricted to a single event, and decreased wheal sizes after the first evocation. Our results indicate that the placebo response in allergy is probably not mainly steered by learning processes but rather by effects of expectation.

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Allostatic Load as a Stress Marker in MONICA/KORA

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Allostatic load (AL) is the burden that is imposed on the body by either chronic or repeated stress or inadequate regulation of stress responses. High AL has been found to be associated with adverse health outcomes such as cardiovascular disease and all-cause mortality.

Here we aimed to develop an AL index as an indicator for repeated or chronic stress to be applied to the population of the KORA S3 survey data. The objective was to assess whether this index was predictive of mortality caused by CHD, CVD or stroke, as well as all-cause mortality. Furthermore we investigated potential interactions of the index with psychosocial factors, for instance job strain or depression.

The study population consisted of 4486 subjects from the population-based KORA study. Using logistic regression, we found that AL was a significant predictor of mortality from cardiovascular disease (OR 1.152, 95 % CI 1.052 – 1.263) and all-cause mortality (OR 1.708, 95 % CI 1.084 – 1.222) in our dataset. Of the psychosocial factors included, only the Social Network Index (SNI) showed to be a significant predictor of mortality from stroke (OR 0.496, 95 % CI 0.280 – 0.878) and all-cause mortality (OR 0.770, 95 % CI 0.663 – 0.893).

Our findings confirm the predictive power of AL for cardiovascular-related disease and mortality. Psychosocial factors do not significantly impact the predictive risk of allostatic load on mortality.

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Placebo-induced immunosuppression in humans: role of learning and expectation

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We analyzed if behaviorally conditioned immunosuppression is affected by the number of re-expositions to the conditioned stimulus (CS) during evocation and whether an immunosuppression can be induced through expectation.

During the acquisition of the conditioning procedure, subjects received the immunosuppressant cyclosporine-A (unconditioned stimulus/US) (n=42) or a placebo (n=23) with a green-colored novel tasting drink (CS) four times. Five days later, participants were re-exposed to the CS paired with placebo pills either four times (n=32) or only once (n=19). Interleukin (IL)-2 production of anti-CD3 stimulated PBMCs was analyzed before and after the acquisition and evocation. Subjects re-exposed four times to the CS during evocation, showed a behaviorally conditioned immunosuppression (significantly decreased IL-2 production). A single re-exposition to the CS did not induce an immunosuppressive effect. Furthermore, we investigated whether an immunosuppression may be induced through expectation. Participants were told to have different probabilities (n=8-9 per condition) of receiving cyclosporine-A but in fact received placebo. We analyzed IL-2 production before the first placebo intake and two hours after the last intake. Expectation did not affect IL-2 production in any group. In conclusion, immunosuppressive effects can be induced through behavioral conditioning (after multiple re-exposures to the CS) but not through expectation.

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Neuroimmunology & Neuroinfectiology in the CNS

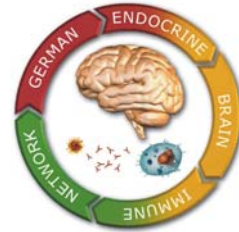
Inhibition of Toll-like receptor 4 (TLR4)-induced NF- κ B activation by NOPr is lost in human glioblastoma cells chronically exposed to LPS

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Glial cells can be activated at multiple sites along the pain pathway to produce pro-inflammatory mediators, thus contributing to the onset and maintenance of neuroinflammation as well as chronic pain states. Toll-like receptor 4 (TLR4) is a glial key activator, responsible for the initial release of pro-inflammatory cytokines. The nociceptin/orphanin FQ peptide receptor (NOPr) is a GPCR which is expressed in neurons, lymphocytes, macrophages and in astrocytes and it is involved in a wide range of physiological responses within the nervous system and the immune system; the release of NOPr endogenous ligand, nociceptin (NC), is significantly increased in different models of neuroinflammation or chronic pain. These findings support a relevant role of NC/NOPr system in neuro-immune and neuron-glia interactions during glial adaptive response to pro-inflammatory stimuli. The aim of this research is to investigate NOPr expression and intracellular signaling in a model of human glial cells, either under basal condition or after exposition to the TLR4 activator, LPS. We found that NOPr activation by NC counteracts TLR4-mediated induction of NF- κ B activation as well as the subsequent release of proinflammatory cytokines. A prolonged exposure (72 h) of glial cells to LPS, significantly down-regulated NOPr mRNA levels through transcriptional processes requiring the activation of p38MAPK. Under these conditions, NOPr-mediated inhibition of TLR4-dependent NF- κ B activation was lost. These findings suggest an important role of NC/NOPr system in balancing glial activation by LPS.

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Experimental endotoxemia as a model to study neuro-immune mechanisms in human visceral and somatic pain

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Although hyperalgesia is a presumed component of sickness behavior, little experimental data exist thus far assessing effects of systemic immune activation on pain in humans. We previously demonstrated that experimentally induced endotoxemia leads to visceral hyperalgesia in healthy humans (*Benson et al., Pain 2012;153(4):794-9*). Based on these initial findings, we designed the present study to complement and extend our knowledge about effects of endotoxemia not only on visceral but also on somatic pain responses.

In this ongoing study, we have implemented a randomized, placebo-controlled between-group design. Following baseline, healthy males receive an intravenous injection of either lipopolysaccharide (LPS group; 0.4 ng/kg) or saline (control group). Visceral sensory and pain thresholds were assessed using pressure-controlled rectal distensions, and somatic pain was induced by pinprick stimulation. Subjective painfulness of rectal and somatic stimuli were evaluated using visual analogue scales. Blood samples were collected before and 1, 2, 3, 4, and 6h after injection to characterize changes in immune parameters including proinflammatory cytokines.

LPS administration induced the expected acute inflammatory response as evidenced by significant increases in circulating TNF-alpha, IL-6, and body temperature (all $p < .001$). Preliminary results show that LPS-treated subjects rated visceral stimuli as significantly more painful compared to controls ($p < .05$), whereas no differences were observed for visceral thresholds and pinprick stimulation.

These findings support the relevance of inflammatory processes in the pathophysiology of human visceral hyperalgesia and underscore the need for studies to further elucidate immune-to-brain communication in chronic pain conditions including the functional gastrointestinal disorders.

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A cytokine network in the brain during synaptic plasticity and learning

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Our previous studies have shown, *in vivo and in vitro*, that long-term potentiation (LTP) induces an NMDA receptor-dependent expression of IL-1 α and IL-6 in the hippocampus. Blockade of the receptors for these cytokines either decreases (IL-1) or supports (IL-6) LTP maintenance, indicating the physiological relevance of their effects. Consistently, interference with IL-1 or IL-6 signalling also restricts or favours, respectively, hippocampus-dependent learning. The question that arises is whether brain-borne cytokines that interact with each other affect learning and memory consolidation just because they have a tonic, permissive effect or because their production increases during learning and are therefore part of the neuro-chemical changes involved in this process, as it occurs during LTP. Here we provide evidence that, besides IL-1 α and IL-6, the endogenous IL-1 receptor antagonist (IL-1ra) and IL-18, but not TNF α , are produced during LTP in freely moving rats. Furthermore, we found that IL-1 α and IL-6 genes are over-expressed in different hippocampal regions soon after learning a hippocampus-dependent alternation task. Restricted changes in IL-18 and no differences in TNF α and IL-1ra expression were noticed in the hippocampus during this learning process, but IL-1ra transcripts were significantly reduced in the prefrontal cortex. These effects were not noticed in pseudo-trained rats that could not learn the task. Taken together with previous studies, we conclude that activation of a cytokine network in the brain is a physiologic relevant condition not only for LTP maintenance but also for the consolidation of the learning process.

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ACE2 drives dendritic cell function and neuroantigen specific immune responses

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The renin-angiotensin system (RAS) is known for its role as a regulator of blood pressure and sodium homeostasis. Its key hormone, Angiotensin II (AngII) also modulates immune function, thereby promoting end organ damage in cardiovascular disease and autoimmune inflammation. Angiotensin converting enzyme 2 (ACE2) is a novel entity within the RAS which antagonizes actions of AngII by cleaving it into Ang1-7. We studied the role of ACE2 in murine experimental autoimmune encephalomyelitis (EAE) a disease model characterized by activation of myelin-reactive T cells that approximates key features of human multiple sclerosis. Unexpectedly, mice that lack ACE2 (ACE2ko) showed ameliorated clinical symptoms of EAE (n = 30 ACE2ko vs 33 ctrl). This was not associated with altered frequencies of splenic CD4+ and CD8+ T cell subsets, NK cells or B cells, but with a slight reduction of CD11c+ dendritic cells (DC; n = 4, p < 0.05). We then tested the capacity of DC lacking ACE2 to induce myelin antigen specific T cell responses in vitro. ACE2 deficiency in DC had no effect on their ability to drive T cell proliferation but reduced their ability to induce FoxP3+ (n = 4, p < 0.001) and IL-17A+ effector T cell subsets from naïve CD4+ T cells by 50% (n = 4, p < 0.001). In summary, ACE2 may constitute a new player in DC function with a pivotal role in driving neuroantigen specific immune responses.

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Experimental endotoxemia as a model to study somatic pain sensitivity in humans

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An enhanced pain sensitivity is one component of sickness behavior in experimental animals. However, data assessing effects of systemic immune activation on pain in humans are scarce thus far. Hence, this study aims to analyze time- and dose-dependent effects of a systemic immune activation on somatic pain responses healthy male volunteers.

In this ongoing study, we implemented a randomized, placebo-controlled between-group design. Following baseline, healthy males received an i.v. injection of either lipopolysaccharide (LPS groups; 0.4 ng/kg or 0.8 ng/kg) or saline (control group). Pain thresholds were assessed by using an Algometer, pinprick stimulation and ice water test. Subjective painfulness of the different stimuli was evaluated using visual analogue scales. The pain-stimulation was performed at baseline, 1 h, 3 h and 6 h after injection. Blood samples are collected before and 1, 2, 3, 4, and 6h after injection to assess changes in proinflammatory cytokines.

LPS administration was followed by a systemic, transient inflammatory response, reflected by significant increases in TNF-alpha, interleukin-6 plasma levels, and body temperature (all $p < .001$). Preliminary results show that LPS-treated subjects rated the somatic pain stimuli as significantly more painful compared to controls ($P < .05$), whereas no differences were observed for pinprick stimulation and ice water.

These observations support the relevance of systemic inflammation in the pathophysiology of human somatic pain sensitivity. Our data suggest differential effects of systemic immune activation on different pain models with most pronounced effects for pressure pain.

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Neuroendocrine Immune Network in Psychiatric Disease

Updating the Mild Encephalitis Hypothesis of Schizophrenia

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Emerging evidence indicates that low level neuroinflammation (LLNI) may not occur infrequently. Many infectious agents with low overall pathogenicity are risk factors for psychoses including schizophrenia and for autoimmune disorders. According to the mild encephalitis (ME) hypothesis, LLNI represents the core pathogenetic mechanism in a schizophrenia subgroup that has syndromal overlap with other psychiatric disorders. ME may be triggered by infections, autoimmunity, toxicity, or trauma. A 'late hit' and gene-environment interaction are required to explain major findings about schizophrenia, and both aspects would be consistent with the ME hypothesis. Preliminary criteria for subgrouping neurodevelopmental, genetic, ME, and other types of schizophrénias were provided. Considering recent investigations of CSF, the ME schizophrenia subgroup may constitute approximately 40% of cases. LLNI may involve dysfunction of the blood-brain barrier, the blood-CSF barrier of CNS-endogenous immunity in part mediated by the volume transmission mode involving CNS-extracellular-fluid and CSF signaling. Both together could represent a common pathogenetic link for the distributed brain dysfunction observed in schizophrenia. However, CSF signaling may even extend along nerves into peripheral tissues via the CSF outflow pathway and explain peripheral topologies of dysfunctions/lesions found (dysautonomia, muscle lesions). In general, CSF signaling including at the PCOP could play an underestimated role in neuroinflammatory disorders.

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Peripheral effects of central serotonin depletion in a mouse model for sub sickness behavior

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Major Depression Disorders (MDD) are the most frequent psychiatric disorders in the Western civilization. The most popular theory highlights the depletion of serotonin (5-HT) and epinephrine in the central nervous system (CNS) as major factors contributing to the development of MDD, while other theories stress the influence of peripheral immune-activation.

Here we used tryptophan hydroxylase2 (TPH2)-deficient mice, that lack the rate-limiting enzyme of 5-HT synthesis in the CNS. We established a model of mild-stimulation of the peripheral immune system by lipopolysaccharide (LPS)-treatment at a dose of 0.02 mg/kg and analyzed the physiological and behavioral responses during four hours after intraperitoneal injection of LPS or saline in *Tph2*-deficient (*Tph2*^{-/-}) and wildtype (*Tph*^{+/+}) mice.

Both *Tph2*^{-/-} and *Tph2*^{+/-} animals displayed typical hypoglycemia and total white blood cell depletion, but no signs of sickness behavior after LPS-administration. However, the increase in corticosterone levels was blunted in *Tph2*^{-/-} mice. FACS analysis showed identical changes in T- and B-cell amounts in blood, bone marrow, and spleen of *Tph2*^{+/-} and *Tph2*^{-/-} animals. Surprisingly, LPS-treated *Tph2*^{-/-} mice were not able to recruit the same amount of Ly6G^{high}/CD115⁺/CD11b⁺/Gr1⁺ progenitor cells from bone marrow as *Tph2*^{+/-} mice and also showed no reduction of these cells in the blood.

Both genotypes showed no signs of sickness or changes in exploration behavior after 4 hours of injection. Evaluation of a depression-like state in the tail suspension test 2 hours after the LPS administration revealed no change in wildtype animals due to treatment, but a decreased level of struggling activity in *Tph2*^{-/-} mice.

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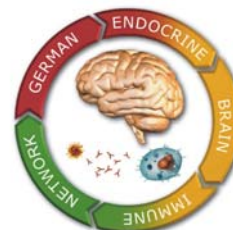
Impact of the immunosuppressant rapamycin on amygdala activity and behavior

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The amygdala, a group of nuclei in the medial temporal lobe, plays an important role in the processing of immune derived signals and the generation of sickness behavior. Here we investigated whether and to what extent treatment with the immunosuppressive drug rapamycin affects amygdala neuronal activity and amygdala-dependent behavior. Rapamycin inhibits the serine/threonine protein kinase mTOR (mammalian target of rapamycin) in T and B lymphocytes and thereby hinders the transition of these cells from G1 to S phase. Our experiments revealed that intraperitoneal administration of rapamycin (3 mg/kg) to adult rats led with a latency of about 90 min to a significant increase in amygdaloid neuronal activity measured by intracerebral electroencephalography as well as to an increase in anxiety-related behavior in the elevated plus maze test. The mechanisms underlying these neuronal and behavioral changes are currently under investigation. Given the pivotal role of the amygdala in mood regulation, associative learning, and modulation of cognitive functions, our findings raise the question whether immunosuppressive therapy may increase the risk for the development of neuropsychiatric diseases.

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Depression und its determinants in patients with rheumatoid arthritis

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Although patients with chronic diseases, including rheumatic diseases, are at the high-risk for symptoms of psychiatric disorders, in clinical practice doctors pay few attentions to those problems.

To investigate the prevalence of depression and related factors in patients with rheumatoid arthritis (RA).

To characterise the pattern of depression in 212 RA patients (mean age 62.5 ± 11.7 , 79% women, 74% seropositive) anxiety questionnaire (STAIT-TRAIT) (Schwenkmezger P., 1989), Beck Depression Inventory (BDI) (Hautzinger M. et al, 1995), painDETECT Test (PDT) (Freyenhagen R., et al., 2006), measurement of pain intensity (visual analogue scale, VAS), multidimensional fatigue inventory (MFI 20) (Lin GM. Et al., 2009), functional assessment of chronic illness therapy (FACIT) (Chandran V. et al., 2007), perceived stress questionnaire (PSQ 30) (Lebenstein S. et al., 1993) as well health assessment questionnaire (HAQ-DI) (Hamilton M., 1980) and short-form health survey (SF 36) (Bullingen M. et al., 1999) were performed.

Depression was presented in 34% RA patients. Married women were less depressive compare to unmarried women ($p = 0.029$). Interestingly, it was a significant correlation between moderate RA disease activity (DAS 3.2 – 5.1) and depression ($p < 0.01$). Otherwise, there is some correlation between pain intensity, as well perceived stress and depression ($p < 0.01$). Furthermore, it was registered an association between symptoms of fatigue and depression ($p < 0.01$), including general fatigue, physical fatigue, reduced motivation and mental fatigue.

Management strategies of depression depending on risk factors should be implemented in the treatment of RA patients with aim to improve the functional outcomes.

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CCL17 deficiency is associated with beneficial CNS immune responses and prevents cognitive decline in a mouse model of Alzheimer's disease

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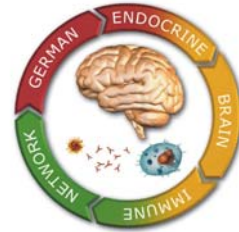
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The CC-chemokine CCL17 regulates leukocyte trafficking during inflammation, however, its role in Alzheimer's disease (AD) pathogenesis remains undefined. This study demonstrated that CCL17 controls Amyloid β ($A\beta$) deposition, neuroinflammation, and cognitive decline in an AD mouse model. CCL17 deficient APP/PS1 mice (APP/PS1-CCL17^{E/E}) showed reduced $A\beta$ brain levels, and were protected against neuronal loss and cognitive deficits. Enhanced microgliosis and brain recruitment of Ly6C⁺CCR2⁺ macrophages expressing mannose receptors associated with elevated brain IL-10 levels pointed to beneficial immune responses in these mice. In the absence of CCL17 we observed accelerated uptake and degradation of $A\beta$, enhanced IL-10 release by activated microglia, reduced expression of the receptor for advanced glycation end products (RAGE) and upregulated $A\beta$ degrading enzyme neprilysin (NEP) in APP/PS1 brains. These newly identified roles for CCL17 in regulating microglia function and memory loss suggest that targeting this chemokine may harbor therapeutic potential for the treatment of AD.

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Quantitative Analysis of the Kynurenine Pathway

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The Kynurenine (KYN) pathway of the tryptophan (TRP) metabolism comprises several highly important key interfaces in the functional interplay between immune system, endocrine system and neurotransmitter system. The first step in this pathway is mediated by two enzymes: TDO and IDO; the activity of TDO is regulated by glucocorticoides, while distinct cytokines are inducers or inhibitors of IDO. T cell tolerance is under control of IDO and the activity of several cells of both, the innate and the adaptive immune system is regulated by the KYN metabolism. On the other hand, several KYN-pathway intermediates are neuroactive, e.g. kynurenic acid (KYNA) is the only known endogenous antagonist at the NMDAR and additionally acts on the $\alpha 7$ nicotinic receptor, while quinolinic acid (QUIN) is an NMDAR agonist and plays a crucial role in the pathophysiology of Alzheimer's disease. However, further progress in the field is limited by the lack of a sensitive and specific method for simultaneous determination of the complete TRP-metabolism.

Therefore, we developed a method for the simultaneous detection of Tryptophan and twelve metabolites in serum, cerebrospinal fluid, tissue homogenate, or cell culture supernatant. The sample preparation is a very cost-effective double-stage protein precipitation. Compared to other methods a very small amount of sample is required, as the sensitive LC-MS/MS technique is used. To increase sensitivity, the metabolites with extremely low concentration undergo an additional derivatisation process. The following analytes are detectable: TRP, 5-HTP, 5-HT, 5-HIAA, KYN, KYNA, 3-HK, 3-HAA, Anthranillic acid, Xanthurenic acid, Quinaldic acid, QUIN and Picolinic acid.

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The anti-inflammatory effects of the 5-HT₃ receptor antagonist tropisetron are mediated by the inhibition of p38 MAPK activation in primary human monocytes

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There is evidence from human and animal research that 5-hydroxytryptamine (5-HT) 3 receptor antagonists, particularly tropisetron, exert analgesic and anti-inflammatory activity. We have demonstrated that tropisetron inhibited lipopolysaccharide (LPS)-stimulated tumor necrosis factor (TNF)alpha and interleukin-(IL-)1beta release in primary human monocytes. The underlying mechanisms of these effects have not been investigated in detail so far.

The molecular mechanisms of the anti-inflammatory effects of tropisetron were investigated in human primary monocytes *in vitro* by studying IL-1beta and TNF- α mRNA levels by PCR and reporter gene assay and by elucidating the phosphorylation of p38 mitogen activated kinase (MAPK) by Western blot.

The steady state levels of IL-1beta and TNF- α mRNA in LPS-activated human peripheral monocytes and the transcriptional activity of the TNF- α promoter were not inhibited by tropisetron, suggesting that the inhibitory activity of this 5-HT₃ receptor antagonist takes place at the post-transcriptional level. Additionally, we found that tropisetron prevents the phosphorylation and thus activation of the p38 MAPK, which is involved in post-transcriptional regulation of various cytokines.

Our data indicate that the anti-inflammatory effects of the 5-HT₃ receptor antagonist tropisetron, as shown *in vivo*, are possibly mediated by a selective inhibition of pro-inflammatory cytokines at the post-transcriptional level. 5-HT₃ receptor antagonists are therefore a new and promising therapeutic option. New and more selective – in respect to the 5-HT₃ subtypes – 5-HT₃R antagonists might be a future perspective in the pharmacological treatment of inflammatory diseases.

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Toll-like receptor pathway in schizophrenia – a pilot study

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Immune response alterations in psychiatric diseases have been discussed repeatedly. The examination of the innate immune system showed alterations of the toll-like receptors (TLR) of schizophrenic patients compared to healthy controls. There was an increased amount of TLRs but decreased responsiveness after stimulation, e.g. with lipopolysaccharides (LPS), in the sense of an endotoxins tolerance, which can be seen as a result of a chronic activation of the immune system. In order to evaluate the TLR changes' impact on the signaling cascade, we analysed the expression of central proteins of the TLR pathway.

In our pilot study we recruited 25 schizophrenic patients and 16 healthy controls. Blood samples were taken once in the control group and twice in the patient group (before and 6-8 weeks after medication with antipsychotics). PBMCs (peripheral blood mononuclear cells) were separated and analysed for the expression of 84 genes of the TLR pathway. The analysis was pooled for the patient and the control group and was conducted before and after stimulation with LPS.

Our results on the mRNA level mostly confirmed results of previous studies on the protein and receptor level. We found a diminished capacity for response after LPS stimulation for factors which activate the TLR pathway. However, there was an increased expression of inhibiting factor of the pathway compared to healthy controls. Differences between the schizophrenic patients and healthy controls will be illustrated using the example of TLRs, MyD88, TOLLIP and IRAK4, in consideration of therapeutic effects of the antipsychotics.

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Posters

CSF outflow along spinal nerves – a neuroradiological document

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Quincke in 1872 demonstrated CSF flowing out from the subarachnoid spaces along nerves into periphery. Meanwhile, CSF outflow through the cribriform plate near olfactory nerves was extensively investigated, poorly along brain nerves and rarely along spinal nerves. From clinical observations it was hypothesized, that CSF may interact at the peripheral CSF outflow pathway (PCOP) with nerves and at wind up in peripheral tissues [1]. It was also demonstrated that leukemia cells followed the PCOP into periphery, e.g. subcutaneous tissues [2]. PCOP associated pathogenetic mechanisms, not proven yet, have the potential to better understand pathogenetic aspects in neuroinflammatory disorders including subgroups of severe psychiatric disorders associated with low level neuroinflammation, e.g. schizophrenia, or in fibromyalgia.

Here, we demonstrate in human subject supposed to lumbar myelography, CSF flowing from the subarachnoid spaces down the lumbar nerves, making a distance of 50.8 mm in 30 minutes. The PCOP hypothesis requires, however, much more research on anatomical details and the variety of pathogenetic questions raised. For example, of outstanding interest was to know more about a possible previously unknown functional link between CSF signaling at the PCOP site and the autonomic nervous system, a connection first described by Quincke but never addressed in specific studies.

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Unfortunately, this contribution did not enter the online version of *Brain Behavior & Immunity* under URL <http://dx.doi.org/10.1016/j.bbi.2013.01.074> because it arrived to late in the office of the organizers.



Effects of mineralocorticoid receptor signaling during sleep on the expression of CD62L and CCR7 on naïve T cells

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Sleep supports adaptive immune functions. However, the underlying mechanisms are still obscure. Animal studies point to a supporting effect of sleep on the migration of T cells to lymph nodes, where adaptive immunity is generated. In line with this assumption, we were able to show in humans that sleep, compared to nocturnal wakefulness, acutely reduces the number of naïve T cells in blood. This effect is likely mediated via mineralocorticoid receptors (MR), the blockade of which mimics the effect of nocturnal wakefulness on cell numbers.

To elucidate the mechanism by which MR signaling affects naïve T cell distribution, we focused on the expression of the 'homing receptor' L-selectin (CD62L) and the chemokine receptor CCR7 that are both essential in the migratory cascade that directs these cells to lymph nodes. To this end, blood from 13 sleeping healthy men was incubated either with an MR agonist (fludrocortisone), an MR antagonist (spironolactone) or PBS as control. After two and four hours of incubation, the expression of CD62L and CCR7 on CD4⁺ and CD8⁺ naïve T cells was examined via flow cytometry.

Preliminary results show that the MR antagonist reduced the expression of both CD62L and CCR7. Accordingly, the agonist slightly increased the expression of CD62L whereas CCR7 levels were unaffected, probably reflecting a ceiling effect due to already high endogenous aldosterone levels. We propose that sleep-dependent activation of MR enhances the migration of naïve T cells from blood to lymph nodes by increasing the expression of CD62L and CCR7 on these cells.

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Quantifying the number and affinity of glucocorticoid receptors in porcine peripheral blood mononuclear cells – establishment of a ligand binding assay

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Glucocorticoids display a central link between the neuroendocrine and the immune system. As they act on leukocytes directly via endogenous glucocorticoid receptors (GR), both the number and affinity of these receptor sites are crucial for the immune-modulating effects of glucocorticoids. Although the pig is considered as suitable model organism for studying the immune system, there is no research concerning GR in porcine leukocytes so far. Moreover, methods allowing their quantification are currently missing. Therefore, this study aimed at the establishment of a method for the quantification of GR number and affinity in porcine peripheral blood mononuclear cells (PBMC).

A ^3H -dexamethasone-based receptor-binding assay adapted for processing in 96-well microtiter plates allowing quantitative analysis of GR in porcine PBMC was established. By calculating the signal to noise ratio using 10^6 PBMC/well a detection limit of 1.5×10^8 total receptor sites and a quantification limit of 7.6×10^8 total receptor sites were found. Evaluation of the intra-assay-precision for quantification of GR number and affinity showed a coefficient of variation of 2.5% and 3.0%, respectively. A range of 1500-2900 GR/cell showing affinities of $K_d=1.4\text{-}3.1$ nM were found for porcine PBMC ($n=15$), thereby closely corresponding to results for human PBMC. Comparing fresh and frozen PBMC probes revealed that PBMC stored at -80°C showed a 13.8% increase in GR number/cell, most probably resulting from a concomitant shift in monocyte to lymphocyte ratios in the frozen probes due to different cell viabilities.

In summary, the established binding assay reliably allows quantification of GR number and affinity in porcine PBMC.

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Recovery of the immune system after hibernation in an obligate hibernator, the edible dormouse

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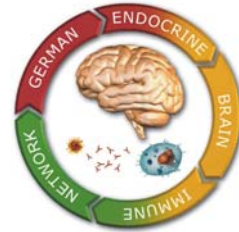
Hibernation and torpor represent the most extreme physiological adaptations of small mammals to reduce energy expenditure during environmentally unfavorable conditions. During hibernation metabolic rate and body temperature are drastically reduced and body temperature can reach values around the freezing point. In ground squirrels (*Spermophilus citellus*) it could be shown, that these extreme physiological states involve severe changes of immune parameters. Accordingly, circulating leukocytes were drastically reduced and a variety of immune functions were impaired during torpor, but recovered immediately afterwards.

The edible dormouse (*Glis glis*) is an obligate hibernator, inhabiting deciduous European woodlands. The aim of this study was to investigate, whether season affects the immune system during the active period of edible dormice.

We therefore captured-mark-recaptured edible dormice in five different study sites in South-Western Germany and took blood samples of 40 adult males between June and September 2012. Flow cytometry and Pappenheim-stained blood smears were used for differential blood cell counts. Leukocyte numbers were determined with a haemocytometer and a Coulter Counter, respectively.

Our results revealed total leukocyte counts that were about twice as high than in other hibernating species, such as ground squirrels. Furthermore, we detected seasonal variations in the proportions of different circulating leukocytes. While lymphocytes clearly dominated (>90%) at the beginning of the active season, proportions of monocytes and neutrophils recovered in the course of the year. A delayed onset of production of innate immune cells may cause this phenomenon and might make edible dormice susceptible to pathogens after hibernation is terminated in early summer.

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Reactivity and cytokine production of T-cells in pregnant sows housed in dynamic groups or single crates

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According to new EU guidelines (2001/88/EC), directing group housing of sows by 2013, mixing of unfamiliar sows will become common practice in intensive pig husbandry. Due to agonistic interactions and hierarchic encounters mixing might lead to social stress, which is known to suppress immune functions. Therefore, the aim of this study was to determine the effects of different housing-systems on the cytokine reactivity of antigen-experienced T-cells, and the antigen-specific T-cell response to a primary immune challenge in pregnant sows.

Blood samples of pregnant sows (German Landrace) either kept in single crates (n=11) or in a dynamic group (n=22) were taken 7, 6, 4, and 2 weeks *pre partum*. Sows were immunized with the neo-antigen keyhole limpet hemocyanin (KLH) 7 and 5 weeks before parturition, respectively. Production of interferon (IFN)- γ and tumor-necrosis-factor (TNF)- α was determined in T-cells by intracellular cytokine staining and assessed by flow cytometry after *in vitro* stimulation with either KLH or phorbol-12-myristate-13-acetate (PMA) and ionomycin.

The frequency of cytokine producing memory T-cells after stimulation with PMA/ionomycin did not differ between sows of the two housing systems. Immunization with KLH evoked a KLH-specific T-cell response without significant effects of the housing conditions. However, whereas KLH-specific IFN- γ and TNF- α double producing T-cells were found already one week after the first immunization in group-housed sows, these cells were not detectable until 3 weeks after the second immunization in single-crated sows.

In summary, these results suggest a more effective immune reaction to primary infections in sows housed in dynamic groups.

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