GEBIN 2017

12th Scientific Meeting
March 23 - 25, 2017
Münster | Germany

Educational Short Course
March 22 – 23, 2017

Dear Colleagues,

On behalf of the Steering Committee of the German Endocrine-Brain-Immune-Network (GEBIN) it is our great pleasure to welcome you to the 12th meeting of the GEBIN that will be held in Münster, March 23-25, 2017.

Since more than 25 years the GEBIN has been a frontier in promoting interdisciplinary research in various fields including anatomy, dermatology, endocrinology, ethology, gynecology, immunology, neurology, pharmacology, psychiatry, psychology, and zoology.

The GEBIN 2017 meeting will be divided into several thematic sessions including one joint session with the research focus group neuro-endocrino-immunology of the German Society for Immunology. Each session will be opened with an introductory key note lecture by an internationally recognized expert in the field. This is followed by short oral presentations selected from submitted abstracts. Poster sessions will also further provide a forum for interactions between GEBIN newcomers and established scientists.

The organizers of the GEBIN Symposium 2017 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 on March 22-23, 2017 and it is intended to present aspects of Behavior-Neuro-Endocrine-Immune interactions on a scholarly level.

We are very much looking forward to welcoming you in the beautiful city of Münster in spring 2017 for the GEBIN 2017 meeting.

With kind regards

Judith Alferink & Markus Böhm

Scientific Committee

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

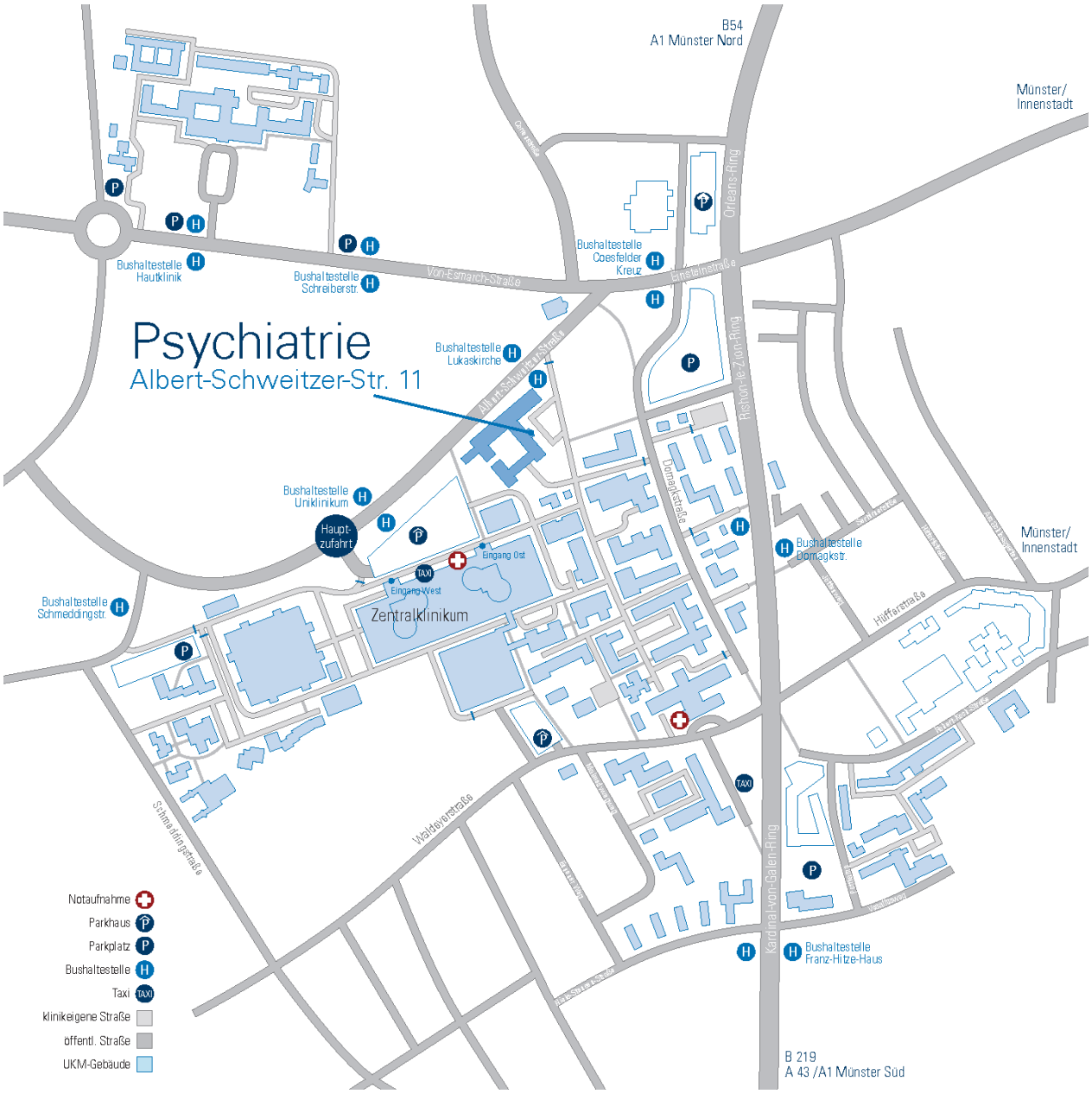
Local Organizing Committee

Judith Alferink
Markus Böhm

Conference Secretary
Bettina Walden
Mara Apel

Congress Venue

Department of Psychiatry and Psychotherapy, University of Münster, Albert-Schweitzer-Campus 1, Building A9, 48149 Münster, Germany. All oral sessions will take place in the Lecture Hall.



Official Language

The official language of the meeting is English.

Registration

Most people already preregistered via the homepage of the meeting: www.gebin-2017.de.
If you wish to register on-site please note that no credit cards but only cash will be accepted.
The on-site registration fee is 150 Euros.

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 22, 2017, 13:30 – 19:00 and March 23, 2017, 09:00 – 13:00.
Venue: Department of Psychiatry and Psychotherapy, University of Münster, Albert-Schweitzer-Campus 1, Building A9, Conference Room, 48149 Münster, Germany.
For further details of the course and for registration, please visit the GEBIN 2017 meeting homepage www.gebin-2017.de or contact Adriana del Rey, Dept. of Physiology, Professor at the University of Marburg, e-mail: delrey@mailer.uni-marburg.de.

Presentations

Contributions are presented in form of short presentations and posters. The time of presentation is 10 min plus 5 min of discussion (= 15 min). Please adhere strictly to this time limit. Presentations should be loaded via USB stick to the presentation computer at least 30 min before the start of the session. Posters should be mounted at the poster walls before the start of the meeting and should be installed throughout the symposium. The surface on the poster board is 90 cm width x 150 cm height. Mounting materials will be provided. Please dismantle your poster after the end of the meeting.

Social Evening

The Social evening will take place on Friday evening, March 24, 2017, from 20:00, in the restaurant Pasta e Basta, Hafenweg 24a, 48155 Münster. Buses will provide transportation from the congress venue to the restaurant after the end of the last session on March 24, 2017.

Hotel Accommodation and Practical Information

For further practical information regarding Münster, transportation, and hotel accommodation please see the GEBIN 2017 meeting homepage www.gebin-2017.de.

Coffee Breaks and Lunch

Coffee, lunch and refreshments are free for all registered participants of the GEBIN 2017 meeting.

Bus Transfer

There will be no specific bus transfer from downtown to the congress venue. The University Hospital and congress venue (bus stop at Lukaskirche or Coesfelder Kreuz) can be easily reached from Münster downtown via several bus lines. For further information see: http://www.stadtwerke-muenster.de/privatkunden/busverkehr/fahrplanauskunft/efa/fahrplanauskunft.html

Main Sponsors / Exhibitors

SERVIER

3000.- €

IMMUNITÄT UND SEELE

2500.- €

abbvie

2000.- €

janssen PHARMACEUTICAL COMPANIES OF Johnson&Johnson

1500.- €

ARISTO

1000.- €

DGfI Deutsche Gesellschaft für Immunologie e.V.

1000.-€

Otsuka

1000.- €

NEURAXPHARM® Ihr Partner für ZNS-Präparate

1000.- €

Supported by

Anatomische Gesellschaft
Arbeitsgemeinschaft Dermatologische Forschung
Deutsche Dermatologische Gesellschaft
Ethologische Gesellschaft
Deutsche Gesellschaft für Biologische Psychiatrie
Deutsche Gesellschaft für Endokrinologie
Deutsche Gesellschaft für Immunologie
Deutsche Gesellschaft für Medizinische Psychologie
Deutsche Gesellschaft für Neurologie
Deutsche Gesellschaft für Pharmakologie
Deutsche Gesellschaft für Psychologie
Deutsche Gesellschaft für Zoologie
PsychoNeuroImmunology Research Society and Brain, Behaviour & Immunity
International Society of Neuroimmunomodulation
The European Neuropeptide Club
World Psychiatric Association, Section Immunology and Psychiatry

Further Information

Further information about the GEBIN can be found at: www.gebin.org. For more information regarding Münster including hotel accommodation please visit the GEBIN 2017 meeting homepage: www.gebin-2017.de.

Program

Educational Short Course

Organized by Adriana del Rey, Marburg
Venue: Department of Psychiatry and Psychotherapy, Conference Room, University of Münster

Wednesday, March 22, 2017

13:30	Check-in
14:00 – 14:30	Introduction and where do the students come from
14:30 – 15:15	Reminding the concept A. del Rey Div. Immunophysiology, Dept. Neurobiology, Philipps University, Marburg
15:15 – 16:00	Immunoimaging: the system in motion W. Kastenmüller Institute of Experimental Immunology, University of Bonn, Bonn
16:00 – 16:30	Coffee Break
16:30 – 17:15	Of hormones, nerves, and autoimmunity: arthritis as an example S. Capellino Leibniz Research Centre for Working Environment and Human Factors, Dortmund
17:15 – 19:00	Students Networking
19:30	Get together dinner: trainee-meet-the-teacher Il Gondoliere, Von-Esmarch-Str. 28, 48149 Münster

Thursday, March 23, 2017

09:00 – 09:45	Cannabinoids as central and peripheral immunomodulators J. Alferink Dept. of Psychiatry, University of Münster, Münster
09:45 – 10:30	Do we need to “complement” neuro-endocrine-immune interactions? W. Schwaeble Dept. of Infection, Immunity and Inflammation, University of Leicester, Leicester
10:30 – 11:00	Coffee Break
11:00 – 11:45	Immunity and obesity H. Sell Leibniz Center for Diabetes Research, Heinrich-Heine-University Düsseldorf, Düsseldorf
11:45 – 12:30	Learning to immunosuppress M. Hadamitzky Inst. of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, Essen
12:30 – 13:00	General discussion and evaluation of the course
13:00	Fin of Educational Short Course

Main Meeting Program

All presentations take place in the Lecture Hall, Dept. of Psychiatry

Thursday, March 23, 2017

14:00 – 17:15 **Neuroinflammation**
Chairs: E. Weihe, Marburg, and H.O. Besedovsky, Marburg

14:00 – 14:10 Address of Welcome:
V. Arolt (Director of the Department of Psychiatry and Psychotherapy, University of Münster)

14.10-14.15 J. Alferink and M. Böhm, Münster (Local Organizers, University of Münster)

14:15 – 15:15 ***Key note lecture*** *(45 talk plus 15 discussion):*
The utility of complement therapeutics in the treatment of neuroinflammatory and neurodegenerative pathologies
W. Schwaeble, Leicester, UK

15:15 – 15:30 **OP01** ONE STEP CLOSER TO THE BRAIN: EFFECTS OF EXPERIMENTAL ENDOTOXEMIA ON CEREBROSPINAL FLUID CYTOKINE CONCENTRATIONS IN HEALTHY HUMANS
H. Engler, Essen

15:30 – 15:45 **OP02** STIMULATION OF THE MELANOCORTIN-1 RECEPTOR LEADS TO DIRECT NEUROPROTECTION IN INFLAMMATORY NEURODEGENERATION
N. Mykicki, Münster

15:45 – 16:15 **COFFEE BREAK**

16:15 – 16:30 **OP03** HIPPOCAMPAL NEURONS AND ITS INFLUENCE ON NEUROIMMUNE INTERACTIONS
L. Fülle, Bonn

16:30 – 16:45 **OP04** THE ROLE OF TETRASPANIN-2 IN NEUROINFLAMMATION AND INNATE IMMUNE RESPONSES
C. Ruland, Münster

16:45 – 17:00 **OP05** IL-17: A MEDIATOR BETWEEN THE IMMUNE SYSTEM AND THE NERVOUS SYSTEM
M. Ebbinghaus, Jena

17:00 – 17:15 **OP06** IL-2 RECEPTOR MODULATION RESTORES IMPAIRED NK-MEDIATED REGULATION OF T-CELL ACTIVITY IN MULTIPLE SCLEROSIS
C. Gross, Münster

17:15 – 17:30 COFFEE BREAK

17:30 – 19:45 Peripheral neuroimmune interactions I
Chairs: R. H. Straub, Regensburg, and T. Lowin, Düsseldorf

17:30 – 18:30 ***Key note lecture*** *(45 talk plus 15 discussion):*
Anatomy of peripheral neuroimmune pathogenesis and disease control – translational perspectives
E. Weihe, Marburg, Germany

18:30 – 18:45 **OP07** AORTA BRAIN CIRCUITS ORGANIZE ATHEROSCLEROSIS IMMUNITY
S. Mohanta, München

18:45-19:00 **OP08** MAST CELL SURVIVAL AND MATURATION IN HUMAN SKIN ARE REGULATED AND MAINTAINED BY SENSORY NERVE FIBERS
J. Chéret, Münster and Manchester

19:00 – 19:15 **OP09** INTRAADRENAL DENDRITIC CELLS INHIBIT CORTICOSTERONE RESPONSE DURING COLLAGEN-INDUCED ARTHRITIS - A ROLE FOR IL-1B AND CXC CHEMOKINES?
H. Stangl, Regensburg

19:15 – 19:30 **OP10** ADHESIVE PROPERTIES OF CYTOMEGALOVIRUS-SPECIFIC T CELLS IN HEALTH AND DISEASE
T. Lange, Lübeck

19:30 – 19:45 **OP11** TNF SENSITIZES RHEUMATOID SYNOVIAL FIBROBLASTS TO TRPA1-MEDIATED CALCIUM FLUX, ANTI-PROLIFERATION AND NECROSIS
T. Lowin, Düsseldorf

19:45 – 21:00 **WELCOME RECEPTION und Poster Session I**
Foyer and Poster Exhibition

19:45 – 20:30 **Meeting of the Steering Committee of the GEBIN**
Conference Room

Friday, March 24, 2017

09:00 – 10:45 **Peripheral neuroimmune interactions II**
Chairs: G. Pongratz, Düsseldorf, and S. Capellino, Dortmund

09:00 – 09:15 **OP12** BODY COMPOSITION AND RESPONSE TO AN IMMUNE CHALLENGE IN NON-OBESE SUBJECTS
K. Boy, Essen

09:15– 09:30 **OP13** DISTRIBUTION PATTERNS OF PHOSPHOLIPID SPECIES IN THE MOUSE VASCULAR ORGAN OF THE LAMINA TERMINALIS DURING SYSTEMIC INFLAMMATION
C. Rummel, Gießen

09:30 – 09:45 **OP14** THE DEBORA PROJECT: EFFECT OF DOPAMINE ON BONE REMODELING IN ARTHRITIS
L. Salinas Tejedor, Dortmund

09:45 – 10:00 **OP15** AUTOANTIBODIES TARGETING MUSCARINIC ACETYLCHOLINE RECEPTORS: IMPLICATIONS ON FATIGUE IN SYSTEMIC SCLEROSIS
S. Sommerlatte, Lübeck

10:00 – 10:15 **OP16** SALIVARY ALPHA-AMYLASE ACTIVITY AND NORADRENALINE RESPONSES TO CORTICOTROPIN-RELEASING HORMONE ADMINISTRATION IN HUMANS
L. Petrakova, Essen

10:15 – 10:30 **OP17** ACTIVATION IN VIVO AND IN VITRO INCREASES RESPONSIVENESS TO CATECHOLAMINES AND REGULATORY POTENTIAL OF B CELLS BY INCREASING IL-10 IN A P38- AND Gi-DEPENDENT MANNER
G. Pongratz, Düsseldorf

10:30 – 10:45 **OP18** OLFACTORY RECEPTOR STIMULATION PROMOTES HUMAN HAIR GROWTH
J. Chéret, Münster

10:45 – 11:00 COFFEE BREAK

11:00 – 13:00 Stress responses and immune function
Chairs: V. Stefanski, Stuttgart, and H. Engler, Essen

11:00 – 12:00 ***Key note lecture*** *(45 talk plus 15 discussion):*
Behavioural profiles are shaped by social experience: when, how and why
N. Sachser, Münster, Germany

12:00 – 12:15 **OP19** RESILIENCE TO SOCIAL STRESS IS ASSOCIATED WITH INCREASED ANTI-INFLAMMATORY ACTIVITY AND IL-17 PRODUCTION BY CD4 T CELLS IN MICE
Oliver Ambrée, Münster and Osnabrück

12:15 – 12:30 **OP20** EFFECTS OF CHRONIC STRESS ON IMMUNE FUNCTION
M. Claus, Dortmund

12:30 – 12:45 **OP21** EFFECTS OF ACADEMIC STRESS ON IMMUNITY
V. Maydych, Bochum

12:45 – 13:00 **OP22** NOREPINEPHRINE MECHANISMS IN PHAGOCYTE REDISTRIBUTION AFTER ACUTE PSYCHOSOCIAL STRESS
D. Beis, Konstanz

13:00 – 14:30 LUNCH und Poster Session II
Foyer and Poster Exhibition Room

14:30 – 16:15 Behavarioural responses and inflammation
Chairs: A. Del Rey, Marburg, and U. Gimsa, Lübeck

14:30 – 14:45 **OP23** EFFECTS OF PRIOR CHRONIC PSYCHOSOCIAL STRESS ON SUBSEQUENT BLUNT THORAX TRAUMA IN MALE MICE
D. Langgartner, Ulm

14:45 – 15:00 **OP24** EFFECTS OF REPEATED MIXING AND SOCIAL STATUS ON BEHAVIOURAL, ENDOCRINE AND IMMUNE RESPONSES OF GROUP-HOUSED PREGNANT SOWS (SUS SCROFA)
C. Schalk, Stuttgart

15:00 – 15:15 **OP25** BEHAVIORALLY CONDITIONED IMMUNOSUPPRESSION REDUCES INFLAMMATORY RESPONSES AND CLINICAL SYMPTOMS IN A MODEL OF RHEUMATOID ARTHRITIS IN RATS
L. Lückemann, Essen

15:15 – 15:30 **OP26** IMPACT OF PSYCHOLOGICAL FACTORS ON PHYSICAL ACTIVITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS
L. Lipovskiy, Leipzig

15:30 – 15:45 **OP27** DIURNAL RHYTHMS OF BLOOD LEUKOCYTES DIFFER BETWEEN LONG DAY AND SHORT DAY CONDITIONS IN DOMESTIC PIGS
L.C. Engert, Stuttgart

15:45 – 16:00 **OP28** SLEEP ENHANCES NUMBERS AND FUNCTION OF MONOCYTES AND IMPROVES BACTERIAL INFECTION OUTCOME IN MICE
J. Hahn, Tübingen

16:00 – 16:15 **OP29** LEARNED T CELL SUPPRESSION IN RENAL TRANSPLANTED PATIENTS
J. Kirchhof, Essen

16:15 – 16:45 **COFFEE BREAK**

16:45 – 19:00 Immune function in mental and psychiatric diseases
Chairs: Alferink, Münster, and N.N.

16:45 – 17:45 ***Keynote lecture*** *(45 talk plus 15 discussion):*
Mechanisms of immune dysfunction in psychiatric disorders
H. Drexhage, Rotterdam, The Netherlands

17:45 – 18:00 **OP30** INFLAMMATORY MONOCYTE GENE EXPRESSION IN MAJOR DEPRESSIVE DISORDER
L. Grosse, Münster

18:00 – 18:15 **OP31** DISTURBED AFFECTIVE COGNITION DURING EXPERIMENTAL ENDOTOXEMIA
S. Benson, Essen

18:15 – 18:30 **OP32** EXPECTATIONS SHAPE THE EMOTIONAL RESPONSE OF EXPERIMENTALLY-INDUCED SICKNESS
J. Lasselin, Essen and Stockholm

18:30 – 18:45 **OP33** METABOLITE FINGERPRINTING REVEALS NEW SERUM METABOLITES AND ASSOCIATED PATHWAYS IN POSTTRAUMATIC STRESS DISORDERS
A. Karabatsiakis, Ulm

18:45 – 19:00 **OP34** INFLAMMATION AND THE BRAIN IN MALTREATMENT AND DEPRESSION: A NEUROIMAGING PERSPECTIVE
R. Redlich, Münster

19:00 – 19:15 **Announcements of GEBIN Prizes and Travel Awards**
V. Stefanski, Stuttgart, J. Alferink and M. Böhm, Münster

20:00 **Social Networking at "Pasta e Basta"**

Saturday, March 25, 2017

09:00 – 12:30 **Neuroendocrinology and immune function**
Chairs: M. Böhm, Münster, and T. Lange, Lübeck

09:30 – 10:30 **Key note lecture** (*45 min talk plus 15 min discussion*):
Immunomodulation by α-MSH and related peptides – Emerging therapies from psoriasis to multiple sclerosis
T. A. Luger, Münster, Germany

10:30 – 10:45 **OP35** STRONG AGE-DEPENDENT EFFECTS OF DOPAMINE ON THE AGGRESSIVE FIBROBLAST PHENOTYPE IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS PATIENTS
L. van Nie, Giessen

10:45 – 11:00 **OP36** IDENTIFICATION OF ANTI-INFLAMMATORY EFFECTS OF OXYTOCIN IN ENDOTOXEMIC MALE RTAS BY HEART RATE VARIABILITY ANALYSIS
G. Pacheco-López, Mexico

11:00 – 11:15 **OP37** THE NEUROPEPTIDE ALPHA-MSH COUNTERACTS UVA-INDUCED OXIDATIVE STRESS IN DERMAL FIBROBLASTS VIA REGULATION OF CATALASE
M. Böhm, Münster

11:15 – 11:45 COFFEE BREAK

11:45 – 12:00 **OP38** NOVEL NEUROENDOCRINE PERSPECTIVES IN HUMAN MELANOCYTE BIOLOGY: VASOACTIVE INTESTINAL PEPTIDE (VIP) REGULATES HUMAN HAIR FOLLICLE PIGMENTATION
M. Bertolini, Münster

12:00 – 12:15 **OP39** ALPHA-MSH ACTIVATES MELANOCORTIN 4 RECEPTOR IN IMMUNE COMPLEXES WITH ALPHA-MSH-REACTIVE PLASMATIC IgG - NEW NEUROIMMUNE MECHANISM OF PEPTIDE SIGNALING ALTERED IN OBESITY AND EATING DISORDERS
S. O. Fetissov, Rouen

12:15 – 12:30 **OP40** ALPHA-MELANOCYTE-STIMULATING HORMONE CONTROLS SKIN CARCINOGENESIS BY INHIBITING THE EXPANSION OF MYELOID-DERIVED SUPPRESSOR CELLS IN A TLR4-DEPENDENT MANNER
N. Mykicki, Münster

12:30 – 12:45 Closing remarks of the GEBIN spokesman and end of the GEBIN Meeting
V. Stefanski, Hohenheim

Abstracts
of the 12th Meeting of the German Endocrine Brain Immune Network (GEBIN)

Short oral presentations

OP01 ONE STEP CLOSER TO THE BRAIN: EFFECTS OF EXPERIMENTAL ENDOTOXEMIA ON CEREBROSPINAL FLUID CYTOKINE CONCENTRATIONS IN HEALTHY HUMANS

H. Engler[1], P. Brendt[2], J. Wischermann[2], A. Wegner[3], R, Röhling[1], T. Schoemberg[4], U. Meyer[5], R. Gold[6], J. Peters[2], S. Benson[1], M. Schedlowski[1]

[1]Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen; [2]Clinic for Anesthesiology and Intensive Care Medicine, University Hospital Essen; [3]Department of Orthopedics and Trauma Surgery, University Hospital Essen; [4]Department of Neurosurgery, University Hospital Essen; [5]Institute of Pharmacology and Toxicology, University of Zurich-Vetsuisse; [6]Department of Neurology, St. Josef-Hospital, Ruhr University Bochum

Systemic inflammation is accompanied by profound behavioral changes (e.g., deterioration in mood, anhedonia, cognitive deficits, fatigue) that show striking similarities with symptoms of depression. Findings in animals suggest that pro-inflammatory cytokines released by activated immune cells in the periphery evoke these behavioral symptoms by driving inflammatory changes in the brain. However, experimental data in humans are lacking. Herein, we show in healthy male volunteers that intravenous administration of low-dose bacterial endotoxin (0.8 ng/kg body weight), a prototypical pathogen-associated molecular pattern that activates the innate immune system, not only induces a significant increase in blood cytokine concentrations (i.e., TNF-α, IL-6, IL-10), but also results in a robust and selective increase of IL-6 in the cerebrospinal fluid (CSF). Moreover, we found a strong association between the endotoxin-induced increase of IL-6 in the CSF and the severity of mood impairment, with larger increases in CSF IL-6 concentration followed by a greater deterioration in mood. Our findings suggest that the appearance of depressive symptoms in inflammatory conditions might be primarily linked to an increase in central IL-6 levels, identifying IL-6 as a potential therapeutic target in mood disorders.

OP02 STIMULATION OF THE MELANOCORTIN-1 RECEPTOR LEADS TO DIRECT NEUROPROTECTION IN INFLAMMATORY NEURODEGENERATION

N. Mykicki[1], A. Herrmann[2], C. Faber[3], H. Wiendl[2], T. A. Luger[1], S. G. Meuth[2], K. Loser[1]

[1]Department of Dermatology, [2]Department of Neurology and 3Institute for Clinical Radiology, University of Münster, 48149 Münster, Germany

In inflammation-associated progressive neurodegenerative disorders, e.g. multiple sclerosis (MS), inflammatory infiltrates, including Th1 and Th17 cells, cause demyelination and axonal/neuronal damage. Regulatory T cells (Treg) control the activation and infiltration of autoreactive T cells into the central nervous system (CNS). However, in experimental autoimmune encephalomyelitis (EAE) and MS, Treg function is severely impaired. Here we demonstrated that Nle4-D-Phe7-α- melanocyte-stimulating hormone (NDP-MSH), by binding to the melanocortin-1 receptor (MC-1R), induced functional Treg, which efficiently inhibited EAE progression. Strikingly, NDP-MSH also prevented immune cell infiltration into the CNS by restoring the integrity of the blood-brain barrier and exerted strong, long-lasting direct neuroprotective effects in an active (MOGimmunization) and spontaneous EAE model (Devic mice). Moreover, NDP-MSH prevented excitotoxic neuronal cell death in isolated mouse as well as human neuronal cells and reestablished action potential firing in embryonic hippocampal neurons. Gene expression studies performed in brain and spinal cord tissue from MOG-immunized and NDP-MSH-treated mice revealed that neuroprotection by NDP-MSH was mediated via signaling through MC-1R, phosphorylation of the cAMP response element-binding protein (CREB) and subsequent activation of the orphan nuclear 4 receptor NR4A1 in mouse and human neurons. NDP-MSH has recently received European Medicines Agency (EMA) approval for the treatment of erythropoietic porphyria and thus, our novel data might support its use in treating neuroinflammatory and neurodegenerative diseases, e.g.

OP03 HIPPOCAMPAL NEURONS AND ITS INFLUENCE ON NEUROIMMUNE INTERACTIONS

L. Fülle[1], N. Offermann[1], J. N. Hansen[2], B. Breithausen[3], L. Radau[1], H. Neumann[4], J. Alferink [5], C. Henneberger[3], H. Weighardt[1], A. Halle [2], I. Förster[1]

[1]Immunology & Environment, Life and Medical Sciences (LIMES) Institute, University of Bonn, Germany; [2]Neuroimmunology, Center of Advanced European Studies and Research (CAESAR), Max Planck Society, Bonn, Germany; [3]Synaptic and glial plasticity lab, Institute of Cellular Neurosciences, University of Bonn Medical School, Germany; [4]Neural Regeneration Group, Institute of Reconstructive Neurobiology, University of Bonn, Germany, [5]Department of Psychiatry, University of Münster, Münster, Germany

It is well known that systemic inflammation alters neuronal function via induction of immune responses in the CNS, including expression of chemokines. Here we show that CCL17, a ligand of CCR4, is expressed in a subset of hippocampal neurons. Expression of CCL17 was analyzed in wild-type and CCL17-EGFP ($CCL17^{E/+}$) reporter mice. Steady-state expression of CCL17 was enhanced by systemic challenge with LPS, but not with CpG or Poly I:C. The LPS-induced CCL17

expression was partly reduced in GM-CSF$^{-/-}$ mice and nearly absent in TNFR$^{-/-}$ mice. Flow cytometric analysis of brain-infiltrating leukocytes following LPS injections revealed reduced numbers of CD45^{+}; CD11b^{+} cells (microglia) in CCL17$^{E/E}$ mice. Furthermore, morphological analysis of Iba-1+ cells in hippocampal sections indicated an altered activation state of microglia from CCL17$^{E/E}$ mice. We also performed electrophysiological recordings on acute brain slices of CCL17$^{E/E}$ mice and observed a slightly altered neuronal signaling in hippocampal CA1 neurons. To investigate the physiological role of CCL17^{+} neurons *in vivo*, CCL17-DTR mice were injected with diphtheria toxin. Depletion of CCL17^{+} neurons was confirmed by histology (TUNEL) and associated with an initial transient loss of body weight and sustained persistent body weight fluctuations. Additionally, increasing numbers of Iba-1^{+} cells in the hippocampal CA1 region were observed. Concurrent with the loss of hippocampal neurons mice showed behavioral abnormalities and sensitivity to stress. In conclusion, CCL17 expression in hippocampal neurons appears to modulate microglial responses to systemic inflammation, while CCL17-DTR mice may be a valuable model system for the analysis of inducible neuroinflammation within the hippocampus.

OP04 THE ROLE OF TETRASPANIN-2 IN NEUROINFLAMMATION AND INNATE IMMUNE RESPONSES C. Ruland[1,2], J. Patzig[3], K. Lahl[4], H. Renken[1,2], A. Fattahi Mehr[1,2], V. Lukacs-Kornek[5], A. Zimmer[6], H. Werner[3], I. Förster[7], T. Sparwasser[8], S. Scheu[9], J. Alferink[1,2]

[1]University of Münster, Department of Psychiatry, Münster, Germany; [2] Cells in Motion, Cluster of Excellence, University of Münster, Münster, Germany; [3]Max-Planck Institute of Experimental Medicine, Department of Neurogenetics, Göttingen, Germany; [4]Technical University of Denmark, Section for Virology, Frederiksberg, Denmark; [5]Saarland University Medical Center, Department of Medicine II, Homburg Germany; [6]University of Bonn, Institute of Molecular Psychiatry, Bonn, Germany; [7]University of Bonn, Department of Immunology and Environment, Limes-Institute, Bonn, Germany; [8]TWINCORE, Center for Experimental and Clinical Infection Research, Institute of Infection Immunology, Hannover, Germany; [9]University of Düsseldorf, Institute of Medical Microbiology and Hospital Hygiene, Düsseldorf, Germany

Tetraspanins modulate migration and responses of immune cells and CNS cells by complex formation with neighboring cell surface proteins. Tetraspanin-2 (Tspan-2) is a member of the tetraspanin family of transmembrane proteins. Up to now, the expression and functional role of murine (m)Tspan-2 in peripheral and CNS immune responses remains unknown. Using a newly generated Tspan-2/DTR/EGFP reporter and a Tspan-2 knockout (Tspan-2$^{-/-}$) mouse model we defined the expression pattern of Tspan-2 and its influence on neuroinflammation and innate immune responses. In the CNS, (m)Tspan-2 was exclusively expressed in mature oligodendrocytes but not found in microglia, astrocytes or neurons. Interestingly, (m)Tspan-2 was upregulated during differentiation of oligodendrocyte precursor cells *in vitro* suggesting a role in oligodendrocyte maturation. *In vivo*, Tspan-2$^{-/-}$ mice exhibited an enhanced clinical severity of experimental autoimmune encephalomyelitis upon immunization with MOG$_{35-55}$

peptide demonstrating that Tspan-2 is functionally involved in CNS autoimmunity. In the peripheral immune system, Tspan-2 expression was found in all neutrophils and a subset of classical dendritic cells in lymphoid organs. LPS treatment of Tspan-$2^{-/-}$ mice increased mRNA levels of TNF, IL-1β, and IL-6 in the spleen. In a model of thioglycollate-induced peritonitis, migration of neutrophils to the peritoneal cavity was markedly enhanced in Tspan-$2^{-/-}$ mice. Tspan$2^{-/-}$ neutrophils further exhibited a reduced accumulation of reactive oxygen species (ROS). These data indicate that (m)Tspan-2 is implicated in ROS production and recruitment of neutrophils, and modulates proinflammatory cytokine responses. Our data provide the first evidence that (m)Tspan-2 is a modulator of innate immunity and inflammatory CNS responses.

OP05 IL-17: A MEDIATOR BETWEEN THE IMMUNE SYSTEM AND THE NERVOUS SYSTEM

M. Ebbinghaus[1], G. Segond von Banchet[1], G. Natura [1], S. Hensellek[1], M. Gajda[2], R. Bräuer[2], H.-G. Schaible[1]

[1]Institute of Physiology 1/Neurophysiology, [2]Institute of Pathology, Jena University Hospital – Friedrich Schiller University of Jena

Objective. Interleukin 17 (IL-17) is supposed to be involved in the pathogenesis of several diseases in the field of musculoskeletal disorders. But its actual impact on mechanisms of inflammation and consequently the therapeutic benefit of IL-17 neutralisation are heterogeneous and still discussed. **Results.** In antigen-induced arthritis (AIA), a murine model of rheumatoid arthritis, we found IL-17A not being essential for the development of inflammation. Wild-type C57BL/6 mice and IL-17KO mice were indistinguishable with respect to joint swelling, infiltration of joints by immune cells and synovial hyperplasia. Also the increase of the release of CGRP, characterizing neurogenic inflammation as an important part in AIA pathogenesis, was present in both groups of mice. Despite this we found IL-17A being involved in the generation of inflammation-evoked pain. In acute AIA mechanical hyperalgesia was reduced in IL-17KO mice. In wild-type mice we could show that all subtypes of IL-17 receptors are expressed in dorsal root ganglia and that IL-17 cytokine family members functionally affect sensory neurons by inducing CGRP release in cell cultures and increasing Na(+) currents in patch-clamp recordings. **Conclusion.** IL-17 potentially contributes to different pathogenic mechanisms. It affects CGRP-mediated neurogenic inflammation and the generation of pain. In AIA the lack of IL-17A ameliorates mechanical hyperalgesia rather than signs of inflammation. Taken together, IL-17 acts as a mediator in the network of neuro-immune interactions. Its possible benefit for disease treatment depends on the significance of these interactions within the pathogenesis.

OP06 IL-2 RECEPTOR MODULATION RESTORES IMPAIRED NK_MEDIATED REGULATION OF T-CELL ACTIVITY IN MULTIPLE SCLEROSIS

C. C. Gross[1], A. Schulte-Mecklenbeck[1], A. Rünzi[1], T. Kuhlmann[2], A. Posevitz-Fejfár[1], N. Schwab[1], T. Schneider-Hohendorf[1], S. Herich[1], K. Held[3], M. Konjević[3], M. Hartwig[1], K. Dornmair[3,4], R. Hohlfeld[3,4], T. Ziemssen[5], L. Klotz[1], S. G. Meuth[1], H. Wiendl[1]

[1]Department of Neurology with Institute for Translational Neurology, University Hospital Münster, Münster D-48149, Germany; [2]Institute of Neuropathology, University Hospital Münster, Münster D-48149, Germany; [3]Institute of Clinical Neuroimmunology, Ludwig Maximilian University, Planegg-Martinsried D-82152, Germany; [4]Munich Cluster for Systems Neurology (SyNergy), München D-81377, Germany; [5]Department of Neurology, University Hospital Dresden, Dresden D-48149, Germany

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system (CNS), resulting from a breakdown in peripheral immune tolerance. Although the importance of immune-regulatory NK-cell functions has recently attracted considerable attention, it still needs to be elucidated whether NK-cell mediated immune-regulation is impaired in MS. Immunohistochemistry revealed occurrence of NK cells in active MS lesions in close proximity to T cells. In accordance to an enrichment of the intrathecal $CD56^{bright}$ NK-cell subset, this NK-cell subset exhibited a higher migratory capacity in an *in vitro* model of the human blood-brain barrier when compared to $CD56^{dim}$ NK cells. Investigating MS patients treated with Natalizumab revealed that transmigration of $CD56^{bright}$ NK cells depends on the $\alpha_4\beta_1$ integrin VLA-4. The migratory capacity of NK-cell subsets derived from MS patients did not differ from the one of healthy individuals. Analysis of immune-regulatory NK-cell functions revealed a reduced cytolytic activity of NK cells derived from MS patients in response to autologous antigen-activated $CD4^+$ T cells, which was mainly due to T-cell evasion caused by impaired DNAM-1/CD155 interaction. In MS, NK cells exhibited a reduced expression of the activating receptor DNAM-1 and $CD4^+$ T cells showed a diminished up-regulation of the DNAM-1 ligand CD155 upon antigen-activation. Therapeutic IL-2 receptor modulation with Daclizumab, not only enhanced the cytolytic activity of NK cells, but also restored the defective NK-mediated immune-regulation by increasing the proportion of CD155 expressing $CD4^+$ T cells. Thus, rendering them more sensitive to NK-mediated lysis.

OP07 AORTA BRAIN CIRCUITS ORGANIZE ATHEROSCLEROSIS IMMUNITY

S. Mohanta[1], L. Peng[2], Y. Li[1], C. Yin[1], T. Mettenleiter[3], R. Straub[4], C. Weber[1], A. Habenicht[1]

[1]Institute for Cardiovascular Prevention, Ludwig-Maximilians-Universität, Munich; [2]Department of Traditional Chinese Medicine, Xiamen University, Xiamen, China; [3]Institute of Molecular Biology, Friedrich Loeffler Institute, Riems; [4]University Hospital Regensburg, Germany

Tertiary lymphoid organs (TLOs) emerge in chronic non-resolving inflammation. Previous studies identified artery TLOs (ATLOs) in the abdominal aorta adventitia of aged apolipoprotein E (ApoE)-deficient mice and ATLOs locally organize atherosclerosis T and B cell immune responses during aging. Peripheral tissue inflammation is known to be affected by the nervous system.

However, the relation between atherosclerosis and the nervous system remains unknown. We reasoned that studies into arterial innervation might possibly uncover novel mechanism for neuronal regulation of cardiovascular physiology during atherosclerosis. We now report on studies in aged ApoE-deficient mice using aorta imaging, flow cytometry, transsynaptic virus tracing, transcript mapping, and chemical sympathectomy: atherosclerosis and ATLOs triggered aorta adventitia neuronal axonogenesis; ATLOs harbored β2-adrenergic receptor - and choline acetyltransferase (ChAT)- expressing immune cells; axons in ATLOs interacted with immune cells including T cells, dendritic cells, and macrophages; atherosclerosis was associated with newly formed T/B cell aggregates near sympathetic ganglia and nerves; peripheral ganglia were infiltrated by T cells, mast cells, and macrophages. Interestingly, atherosclerotic artery segments were wired to distinct brainstem and hypothalamus nuclei through sympathetic and sensory ganglia axons via thoracic spinal cord segments T6-T12. Moreover, chemical sympathectomy for four weeks in young mice increased atherosclerosis without altering cardiac functions. These data reveal that ATLOs form neuroimmune circuits with the central nervous system called aorta brain circuits that might organize immune responses in atherosclerosis.

OP08 MAST CELL SURVIVAL AND MATURATION IN HUMAN SKIN ARE REGULATED AND MAINTAINED BY SENSORY NERVE FIBERS

J. Chéret[1,3], L. Ponce[1], C. Le Gall-Ianotto[3], L. Misery[3], M. Bertolini[1,2], R. Paus[4].

[1]Monasterium Laboratory, Münster, Germany, [2]University of Münster, Münster, Germany, [3]University of Western Brittany, Brest, France, [4]University of Manchester, Manchester, United Kingdom

Although adult human skin (HS) harbors resident mast cell (MC) progenitors (rePro), how intracutaneous MC maturation from rePro is regulated is only very incompletely understood. Since nerve fiber (NF)-derived stimuli can promote MC maturation from rePro in murine skin, we investigated whether this also happens in experimentally reinnervated HS *ex vivo*, using a model where HS is co-cultured with primary sensory neurons from rat dorsal root ganglia. Here, we show that the presence of PGP9.5+/MBP+ rat NFs significantly promotes the survival of both immature (c-Kit+) and mature (tryptase+) MCs in HS *ex vivo* without affecting MC degranulation. Interestingly, the number and percentage of c-Kit$^+$/tryptase$^+$ cells further increased during HS organ culture, despite MC proliferation and apoptosis being largely unaffected. This suggests that signals secreted by rat sensory NFs promote the maturation of tryptase+ MCs from tryptase-/c-kit+ MC rePro *in situ*. Intriguingly, immunofluorescence microscopy also revealed that rat MBP$^+$-NFs, which are positive for different neuromediators, weave a cage-like structure around HS MCs *ex vivo,* suggesting that MCs can guide HS innervation. These preliminary data suggest that the release of neurotrophins and/or neuropeptides by myelinated sensory NFs and are involved in intracutaneous MC maturation from rePro and MC homeostasis in healthy HS.

OP09 INTRAADRENAL DENDRITIC CELLS INHIBIT CORTICOSTERONE RESPONSE DURING COLLAGEN-INDUCED ARTHRITIS - A ROLE FOR IL-1B AND CXC CHEMOKINES?

H. Stangl, C. Wolff, M. Lesiak, R. H. Straub

University Hospital Regensburg, Lab. of Experimental Rheumatology, Regensburg, Germany

In rheumatoid arthritis (RA) and collagen-induced arthritis (CIA) the phenomenon of a relative insufficiency of adrenal glands to produce an adequate amount of glucocorticoids in later stages of the disease is well known (Spiess et al., Wolff et al.). Additionally, the presence and migration of macrophages and dendritic cells (DCs) in and into the pituitary and adrenal gland (AG) has been described (Glennon et al., Sato, Engstrom et al.). We hypothesized that these cells contribute to the inadequate glucocorticoid secretion during RA. CIA was induced in DA rats. Cytokines in supernatants (SN) from whole AG cells, bone marrow-derived DCs, and the corticosterone secretion from AG cells in co-culture with DCs were quantified with ELISA. Analysis of SN revealed a similar profile of the C-X-C ligand chemokines CINC-1,-2,-3 (Cytokine-induced neutrophil chemoattractant), LIX (LPS-induced CXC chemokine) and of the cytokine IL-1β in SN from DCs and AG cells. DCs generated from arthritic rats expressed significantly more IL-1β, CINC-1,-2,-3, and LIX (all $p<0.001$) compared to controls. Levels of IL-1β ($p<0.001$) and CINC-2 ($p=0.034$) in SN from arthritic AG cells were significantly higher compared to controls. Co-culture experiments revealed an inhibitory effect of DCs from control and arthritic rats on the corticosterone response of AG cells. DCs are present in adrenal glands and seem to inhibit corticosterone production, possibly via IL-1β, CINC-1,-2,-3 and LIX. Specific targeting of these cells and chemokines might prevent relative adrenal gland insufficiency during arthritis and, hence, could be a future therapy.

OP10 ADHESIVE PROPERTIES OF CYTOMEGALOVIRUS-SPECIFIC T CELLS IN HEALTH AND DISEASE

T. Lange[1], G. Balsen[1], A. Müller[1], G. Riemekasten[1], J. Born[2,3,4], L. Besedovsky[2], S. Dimitrov[2,3,4]

[1]Clinic for Rheumatology and Clinical Immunology, University of Lübeck; [2]Department of Medical Psychology and Behavioral Neurobiology, University of Tübingen; [3]German Center for Diabetes Research (DZD), Tübingen; [4]Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen (IDM)

A crucial step in T-cell adhesion is the activation of beta2-integrins (e.g., lymphocyte function-associated antigen (LFA)-1) that allows firm binding to the respective ligand intercellular adhesion molecule (ICAM)-1 on antigen-presenting cells, target cells or endothelial cells. On resting T cells beta2-integrins are inactivated, but chemokines such as fractalkine (CX3CL1), cytokines like tumor necrosis factor (TNF) and T-cell receptor (TCR) stimulation can induce inside-out signaling with unbending and clustering of beta2-integrins on the surface of T cells, which increases their avidity for ICAM-1. By means of a new, fast flow cytometry assay we detected rapid beta2-integrin activation on the majority of cytomegalovirus (CMV)-specific T cells upon antigen-specific TCR stimulation and these T cells showed high markers of

cytotoxicity. Epinephrine attenuated this TCR-triggered beta2-integrin activation in a dose-dependent manner, presumably via the beta2-adrenoceptor that can block inside-out signaling by increasing intracellular cyclic adenosine monophosphate (cAMP). As enhanced adhesion of CMV-specific T cells can induce endothelial damage, short-term increases in epinephrine and subsequent T cell de-adhesion might contribute to the anti-inflammatory effects of physical activity. In the clinical setting, we now elaborate adhesive properties of CMV-specific T cells in patients with systemic sclerosis, an autoimmune disease that is characterized by obliterative vasculopathy. We hypothesize that increased CX3CL1 and TNF signaling and/or repeated TCR stimulation in these patients promotes beta2-integrin activation and adhesion of CMV-specific T cells with subsequent endothelial apoptosis and that beneficial therapeutic effects of prostanoids stem from increases in intracellular cAMP and T cell de-adhesion.

OP11 TNF SENSITIZES RHEUMATOID SYNOVIAL FIBROBLASTS TO TRPA1-MEDIATED CALCIUM FLUX, ANTI-PROLIFERATION AND NECROSIS

T. Lowin[1], R. H. Straub[2] and G. Pongratz[1]

[1]Poliklinik, Funktionsbereich & Hiller Forschungszentrum für Rheumatologie, University Hospital Duesseldorf, 40225 Duesseldorf, Germany; [2]Dept. of Internal Medicine I, University Hospital Regensburg, 93042 Regensburg, Germany

Background: Transient receptor potential type ankyrin (TRPA1) is a nociceptive ion channel mainly expressed on sensory neurons but also in non-neuronal cells such as rheumatoid arthritis synovial fibroblasts (RASF). RASF are one main contributor of joint destruction as they resist apoptosis and secrete pro-inflammatory cytokines. Since TRPA1 knockout mice developed only mild arthritis, we investigated the effect of TRPA1 activation and inhibition on the function of RASF under normal and inflammatory conditions. **Methods:** TRPA1 was detected by immunocytochemistry and western blot. Calcium signals were determined fluorometrically. Cell viability was assessed by quantification of lactate dehydrogenase (LDH) in culture supernatants. IL-6 and IL-8 were determined by ELISA. Proliferation was determined by cell titer blue incorporation. **Results:** TNF up-regulated TRPA1 protein levels in RASF which was accompanied by increased sensitivity to the TRPA1 agonists allylisothiocyanate (AITC) and polygodial in several assays. Calcium flux and lactate dehydrogenase release (a marker for necrosis) were increased with TNF-induced up-regulation of TRPA1 while overall cell viability decreased. TNF not only reduced the threshold of AITC and polygodial but also led to a faster onset of TRPA1-mediated effects. In addition, secretion of IL-6 and IL-8 was attenuated by TRPA1 agonists, although mainly through inhibiting cell survival. **Conclusion:** TNF up-regulates and sensitizes TRPA1 in RASF. Subsequent activation of TRPA1 increased calcium flux and reduced cell viability. Since TRPA1 agonists showed exacerbated effects in TNF stimulated RASF, this cation channel might an attractive therapeutic target in chronic inflammation to reduce the activity of pro-inflammatory SF in the joint.

OP12 BODY COMPOSITION AND RESPONSE TO AN IMMUNE CHALLENGE IN NON-OBESE SUBJECTS

K. Boy[1], M. Lekander[2], M. J Olsson[2], S. Paues-Göranson[2], J. Axelsson[2], M. Schedlowski[1], J. Lasselin[1,2]

[1]Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, Germany, [2]Dept. of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

A higher level of adiposity is associated with increased risk for physiological and psychiatric diseases. One possible underlying mechanism is the alteration of immune processes, which are induced by modifications of adipose tissue functions. Inflammatory factors like cytokines can interact with the brain activity, resulting in behavioral and mood alterations. Nevertheless, it is still unclear whether the level of adiposity modulates these immune-related processes already in non-obese subjects. The aim of this study was therefore to assess the impact of the percentage of body fat on the immune response and on the subsequent behavioral and mood symptoms after an immune challenge. To this aim, we examined the effect of body composition on body temperature, pro-inflammatory cytokine concentrations in plasma (IL-6, TNF-α) and behavioral changes (sickness symptoms, state anxiety) after an immune challenge using a bacterial stimulus (intravenous injection with lipopolysaccharide, LPS) in 22 non-obese subjects. The percentage of body fat and trunk fat was assessed using an impedance meter. Injecting LPS induced a significant increase in body temperature, pro-inflammatory cytokines and behavioral symptoms compared to an injection with placebo. No evident association of body composition with body temperature, pro-inflammatory cytokine and behavioral symptom responses was found. These data suggest that the percentage of body fat or trunk fat does not have a strong impact on the named measures after an immune challenge in healthy, non-obese subjects. Studies with greater ranges in body fat are needed to further elucidate the influence of body composition on the response to an immune challenge.

OP13 DISTRIBUTION PATTERNS OF PHOSPHOLIPID SPECIES IN THE MOUSE VASCULAR ORGAN OF THE LAMINA TERMINALIS DURING SYSTEMIC INFLAMMATION

J. Bredehöft[1], D. Ram Bhandari[2], V. Peek[1], B. Spengler[2], S. Schulz[2], K. Mayer[3], J. Roth[1], Ch. Rummel[1]

[1]Institute of Veterinary Physiology and Biochemistry, Justus Liebig University Gießen; [2]Institute of Inorganic and Analytical Chemistry, Justus Liebig University Gießen; [3]Department of Internal Medicine, Justus Liebig University Gießen

Omega-3 fatty acids (3-FAs) can contribute to active resolution of inflammation and brain-controlled febrile responses during inflammation. However, knowledge about the distribution of 3-FA-carrying lipids (e.g. phosphatidylcholine, PC) and potential changes during inflammation in the brain is sparse. Here, we aimed to characterize the distribution and relative concentration of several lipids in a brain structure important for immune-to-brain communication, namely the vascular organ of the lamina terminalis (OVLT), during systemic lipopolysaccharide (LPS)-

induced inflammation. For this purpose, wild type and fat-1 transgenic mice, which produce large quantities of omega 3-FA endogenously, were stimulated with LPS (i.p., 2.5mg/kg) or PBS. Animals were sacrificed (24h); brains and blood samples were collected and analyzed by immunohistochemistry, high-resolution atmospheric-pressure scanning microprobe matrix assisted laser desorption/ionization ion source combined with an orbital trapping mass spectrometer and bioassays, respectively. Telemetric recordings revealed enhanced hypothermia in LPS-treated fat-1 mice compared to wildtype controls. Moreover, depending on genotypes and treatment, several distinct distribution patterns were observed at the level of the OVLT and surrounding tissue for phospholipids [e.g. PC(38:6), LysoPC(16:0)/(18:0), PE(P36:4)]. These patterns included equal distributions, accumulation or absence within the OVLT compared to adjacent brain tissue. A localized increase of LPCs was indicative of enhanced LPS-induced turnover of fatty acid metabolism in the OVLT in fat-1 mice compared to wild type controls. Overall, the lipid distribution patterns in the OVLT are different from surrounding brain areas and change with inflammation. Their precise role for brain inflammation remains to be further investigated.

OP14 THE DEBORA PROJECT: EFFECT OF DOPAMINE ON BONE REMODELING IN ARTHRITIS

L. Salinas Tejedor[1], S. Rehart[2], E. Neumann[3], C. Watzl[1], U. Müller-Ladner[3],S. Capellino[1]

[1]Department of Immunology, Leibniz research center for working environment and human factors Dortmund; [2]Department of Orthopedics and Trauma surgery, Agaplesion Markus hospital, Frankfurt; [3]Department of Internal Medicine and Rheumatology, Justus-Liebig-University Gießen, Kerckhoff-Klinik, Bad Nauheim

Background: Rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic joint inflammation and systemic osteoporosis. Current therapies do not prevent permanently loss of bone mass nor achieve bone repair. Therefore, new therapeutic alternatives that could enhance bone formation are necessary. The aim of this EU-funded project is to understand the role of Dopamine (DA) in bone metabolism and to identify a potential therapeutic target that could control bone erosion. **Methods:** Bone tissue from osteoarthritis (OA) and RA patients were paraffin-embedded for Immunohistochemical analysis. Localization of dopamine receptors (DR) subtypes were evaluated in several areas, such as cartilage/bone interface, trabecular bone and remodeling area, as well as in isolated osteoblasts (OB) and osteoclasts (OC). Additionally, isolated OB were cultured in vitro and pre-treated with TNFα for 24h. After medium exchange, DR agonists (Fenoldopam and Ropinirole) were added for additional 24h. IL-6, IL-8, CCL20 and Pro-MMP1 were quantified by ELISA. Tyrosine hydroxylase (TH) expression was measured by RT-PCR. **Results:** DR subtypes D1 to D5 were detected in the cartilage/bone interface of RA patients, D3 and D5 receptor were localized in trabecular bone and D1, D3, D4 could be observed in remodeling area of RA patients. After isolation, OB maintained DR expression and TH production. Moreover, treatment with D1-like DR agonist promotes the production of IL6, whereas D2-like DR stimulation seems to increase the synthesis of CCL20 and Pro-MMP1.

Discussion: Dopamine receptors are upregulated during inflammatory conditions in RA osteoblasts and their activation seems to promote bone resorption in an autocrine/paracrine manner.

OP15 AUTOANTIBODIES TARGETING MUSCARINIC ACETYLCHOLINE RECEPTORS: IMPLICATIONS ON FATIGUE IN SYSTEMIC SCLEROSIS

S. Sommerlatte[1], H. Bittern[1], S. Pitann[1], G. Marschner[1], A. Müller[1], O. Cabral-Marques[1], H.Heidecke[2], T. Lange[1], G. Riemekasten[1]

[1]Department of Rheumatology, University of Lübeck; [2]CellTrend GmbH, Luckenwalde

Background: Muscarinic acetylcholine receptors (mAChR) are neuroimmune G protein-coupled receptors comprising 5 subtypes (M1-M5). Autoantibodies recognizing mAChRs have been linked to chronic fatigue syndrome. Fatigue is common in patients with autoimmune diseases such as systemic sclerosis (SSc). **Objective and Methods:** In a first study, we analyzed autoantibodies targeting M1-M5 in 113 SSc patients and 113 sex- and age-matched healthy controls by ELISA. In an ongoing second study we investigate frequency and severity of fatigue (brief fatigue inventory, multidimensional fatigue inventory 20, fatigue severity scale), depression (patient health questionnaire-9), pain (German pain questionnaire), sleepiness (Epworth sleepiness scale), sleep quality (Pittsburgh sleep quality index) and chronotype (Munich chronotype questionnaire) in relation to anti-M1-M5 autoantibodies in 100 SSc patients. **Results:** In the first study we found significantly decreased levels of autoantibodies targeting M2, M4 and M5 in SSc patients compared to healthy controls. In the second study, 54 SSc patients completed the questionnaires until now. 24% of these patients suffered from severe fatigue and 49% felt unusually fatigued during the last week. 33% showed at least mild depression, 52% enhanced sleepiness and 61% poor sleep quality. Fatigue correlated with depression and sleepiness. Data on chronotype and autoantibodies are currently under analysis. **Conclusion:** Our findings demonstrate a high frequency of fatigue, depression, sleepiness and poor sleep in SSc patients. Altered patterns of autoantibodies targeting mAChR may contribute to the pathogenesis of fatigue in SSc and potentially offer new therapeutic possibilities.

OP16 SALIVARY ALPHA-AMYLASE ACTIVITY AND NORADRENALINE RESPONSES TO CORTICOTROPIN-RELEASING HORMONE ADMINISTRATION IN HUMANS

L. Petrakova[1], K. Boy[1], L. Mittmann[1], L. Möller[2], H. Engler[1], M. Schedlowski[1]

[1]Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, 45122 Essen, Germany; [2]Clinic for Endocrinology, University Hospital Essen, University of Duisburg-Essen, 45122 Essen, Germany

Salivary alpha-amylase (sAA) is a digestive enzyme that hydrolyzes starch and glycogen. It is produced by the salivary glands under the control of the autonomic nervous system. Marked increases in sAA activity were observed in response to various stressors, leading to the assumption that sAA activity may be used as a surrogate marker of sympathetic activation.

However the reliability of this marker and its association with noradrenaline and other indicators of sympathetic activation remain unclear. In the present study we activated the sympathetic nervous system using the corticotropin-releasing hormone (CRH) stimulation test and assessed noradrenaline and sAA response. Thirty one healthy male volunteers received an injection of CRH (100 µg) or placebo in a randomized order. Blood and saliva measures were analyzed at baseline and 15, 30, 60, 120 min after injection. Results showed that CRH administration increased both noradrenaline and sAA activity levels, and in the CRH group the total increase of sAA activity significantly correlated with noradrenaline release. However, the two parameters did not correlate with each other at any time point measured, indicating both sAA and plasma noradrenaline as reliable but distinct markers of sympathetic activation in pharmacological challenge paradigm.

OP17 ACTIVATION *IN VIVO* AND *IN VITRO* INCREASES RESPONSIVENESS TO CATECHOLAMINES AND REGULATORY POTENTIAL OF B CELLS BY INCREASING IL-10 IN A P38- AND Gi-DEPENDENT MANNER

G. Pongratz[1], B. Opgenoorth[1], R. Straub[2], M. Schneider[1], T. Lowin[1]

[1]Department of Rheumatology & Hiller Research Center Rheumatology, University Hospital Düsseldorf; [2]Lab. for Exp. Rheumatology and NeuroEndocrinoImmunology, University Hospital Regensburg;

Background: Splenic B cells from collagen-induced arthritis (CIA) mice react to a β2adrenoceptor (AR) stimulus with increased IL-10 production and adoptive transfer of these cells decreases disease activity. However, B cells from unimmunized mice do not adequately increase IL-10. Therefore, we test the hypothesis that sensitivity to catecholamines changes during CIA and try to mimic changes that have to occur *in vivo*, in the *in vitro* setting with the goal to increase regulatory potential of B cells *in vitro*. **Methods:** FACS, ELISA, Western Blot, human and mouse B cell culture, CIA **Results:** In the course of CIA the percentage of β2-AR+ B cells increased (ANOVA $p<0.05$), G-protein coupled receptor kinase (GRK2) decreased from day 6 p.i. (ANOVA $p<0.0001$), and phosphorylation of p38 (ANOVA $p<0.001$) and cAMP-responsive element binding protein (CREB, ANOVA $p<0.001$) following a β2-AR stimulus is augmented in late CIA. Responsiveness to catecholamines can also be increased in vitro by unspecific, T cell independent stimuli to naive murine B cells, which increases ARs and leads to increased, p38-dependent IL-10 production. Interestingly, the catecholamine induced IL-10 increase can be blocked by pertussis toxin, a Gi Protein antagonist, pointing to β-arrestin rather than cAMP-dependent mechanism. **Conclusion:** The current data show, that B cells increase catecholamine responsiveness via increased AR and downregulated GRK2 in the course of CIA and after T cell independent activation, favoring p38-dependent and Gi-dependent mechanisms that increase IL-10. Defining key players in this complex regulatory mechanism might lead to new therapeutic strategies in autoimmune diseases.

OP18 OLFACTORY RECEPTOR STIMULATION PROMOTES HUMAN HAIR GROWTH

J. Chéret[1], L. Ponce[1], M. Bertolini[1,2], T. Tsai[3], M. Alam[1], H. Hatt[3], R. Paus[4].

[1]Monasterium Laboratory, Münster, Germany; [2]University of Muenster, Muenster, Germany; [3]Ruhr-University Bochum, Bochum, Germany; [4]Univisersity of Manchester, Manchester, UK.

Chemical signals acting on olfactory receptors (OR) regulate many cell functions beyond olfaction, e.g. OR2AT4-mediated keratinocyte (kerat) proliferation and migration *in vitro.* Here, we asked whether OR2AT4 also plays a role in human hair follicle (hHF) biology. Indeed, anagen scalp hHFs prominently express OR2AT4 protein (IF) in the central outer root sheath, and up-regulate OR2AT4 transcription (qRT-PCR) after stimulation with a specific OR2AT4 agonist, Sandalore®. Sandalore® significantly retarded spontaneous catagen development in anagen HFs *ex vivo* and decreased the number of apoptotic (TUNEL+ or caspase-3+)hair matrix (HM) kerat compared to controls. These effects were partially counteracted by coadministering the specific OR2AT4 antagonist, Phenirat®. Most importantly, catagen was induced prematurely and HM kerat apoptosis was enhanced in OR2AT4-silenced hHFs, compared to vehicle HFs, even under Sandalore® stimulation. Sandalore® significantly decreased TGFβ2 expression, but significantly increased IGF-1. OR2AT4 knock-down decreased IGF-1 expression while TGFβ2 expression was unchanged, suggesting that OR2AT4 activation impacts on HF cycling via up-regulating IGF-1. Microarray analysis showed that Sandalore® significantly downregulated the transcription of pro-apoptotic and up-regulated anti-apoptotic genes. By phosphokinase assay, phosphorylation of kinases involved in the IGF-1 pathway was enhanced under Sandalore® stimulation. In summary, we show for the first time that hHFs engage in OR-mediated chemosensation and that OR2AT4 stimulation is required to maintain hHFs in anagen *ex vivo*. This suggests that OR2AT4 ligands like Sandalore® can be recruited for the management of hHF growth disorders.

OP19 RESILIENCE TO SOCIAL STRESS IS ASSOCIATED WITH INCREASED ANTI-INFLAMMATORY ACTIVITY AND IL-17 PRODUCTION BY CD4 T CELLS IN MICE

O. Ambrée[1,2], C. Ruland[2], P. Zwanzger[3], L. Klotz[4], V. Arolt[2], S. Scheu[5], J. Alferink[1,6]

[1]Dept. of Psychiatry, University of Münster; [2]Dept. of Behavioural Biology, University of Osnabrück; [3]kbo-Inn-Salzach-Klinikum, Wasserburg am Inn, [4]Dept. of Neurology, University of Münster, [5]Institute of Medical Microbiology and Hospital Hygiene, University of Düsseldorf, [6]Cluster of Excellence EXC 1003, Cells in Motion, University of Münster

Chronic stress is a risk factor for the development of depression. Both, stress and depression involve long-term alterations of adaptive immune responses. However, it is yet unknown whether stress-induced immune alterations differ in stress susceptible and resilient individuals. The aim of this study was to elucidate whether susceptibility and resilience are associated with characteristic T cell responses in the social defeat model of depression. After 10 daily social defeats, C57BL/6J mice were tested for social avoidance. Expression levels of immune-related genes were assessed in the spleen, and cytokine-producing splenic T cells analyzed by flow cytometry. Both, susceptible and resilient mice exhibited reduced CD4 T cell counts compared

to controls. Moreover, expression levels of Th1-associated genes *Il12a* and *Ifng* were reduced. Expression levels of the *Il17f* gene, encoding the Th17 cytokine IL-17, were enhanced in these animals. Consistently, mRNA levels of *Il27*, encoding the Th17 cell-suppressing cytokine IL-27, were decreased. At the cellular level, only resilient mice showed increased percentages of IL-17-producing CD4 T cells, which have been shown before to promote depression-like behavior but have recently also been implicated in the maintenance of brain integrity. Importantly, resilient mice further exhibited enhanced numbers of CD4 T cells producing the anti-inflammatory cytokine IL-10, and higher *Tgfb2* expression, encoding the immunoregulatory transforming growth factor-β. In summary, our findings demonstrate an altered T cell homeostasis after social defeat and T cell-mediated anti-inflammatory actions exclusively in stress resilient animals. These results suggest that a delicate balance between pro- and anti-inflammatory responses might influence stress-induced depression-like behavior.

OP20 EFFECTS OF CHRONIC STRESS ON IMMUNE FUNCTION

M. Claus, P. Bröde, P. Gajewski, S. Getzmann, M. Falkenstein, C. Watzl

Leibniz Research Centre for working environment and human factors - IfADo, Dortmund, Germany

It is well established that chronic stress interferes with normal immune function. Further, persistent strain in stressful occupations negatively affects psychological parameters and can even lead to the development of depression or burnout, which in turn affect immune function. Therefore, the main goal of our study was the determination of immunological parameters which reliably describe the reactions and adaptations to chronic stress in relation to burnout symptoms or depressivity. We further aimed to identify correlations between immunological and psychological responses to stress. The effects of chronic stress were studied in 76 employees working in mentally stressful occupations. We found strong correlations of several immune parameters with age and gender. In analyses corrected for gender and age, high scores for depressivity and emotional exhaustion correlated with increased proinflammatory cytokines like IL-6 and IL-12 and CD28 negative T cells, which are found in chronic inflammation and immune aging. Interestingly, increased amounts of proinflammatory cytokines and aged T cells also correlated with reduced cognitive performance. The findings of our study suggest that immune function and cognition are differentially affected by chronic stress, and that cognitive performance is correlated with inflammation and immune aging.

OP21 EFFECTS OF ACADEMIC STRESS ON IMMUNITY

V. Maydych[1], M. Claus[1], C. Watzl[1], T. Kleinsorge[2], O. T. Wolf[3]

[1]Department of Immunology, Leibniz Research Centre for Working Environment and Human Factors, [2]Department of Psychology & Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, [3]Department of Cognitive Psychology, Ruhr University of Bochum

There exists convincing evidence linking psychological stress to immunological changes. This study investigated effects of academic stress and chronic stress on several immune parameters and cortisol. The sample consisted of 20 students taking academic examinations. Blood and saliva samples were collected five times over eight weeks. Examinations elicited significant changes in the numbers of NK cells, monocytes, and the percentages of several NK and T cell subsets by all students. For NK cells and NK CD57+ cells the magnitude and pattern of changes differed between chronically stressed and non-stressed individuals. Further, chronic stress was negatively associated with the percentages of T CD8 effector and central memory cells, and positively associated with the percentages of naïve T CD8 cells and serum levels of interleukin 17 (IL-17). In contrast with previous research, our data suggest that academic examinations had little systematic relationships with functional immune parameters. They did, however, have effects on enumerative immune measures, particularly the percentages of cell subsets reflecting the maturation status of NK and T cells. Chronic stress partially moderated theses effects indicating lower amounts of cells and damped responsiveness to stress in chronically stressed individuals. Together these findings suggest that depending on the parameter academic stress has both enhancing and suppressive effects on immunity leading to an immune dysregulation.

OP22 NOREPINEPHRINE MECHANISMS IN PHAGOCYTE REDISTRIBUTION AFTER ACUTE PSYCHOSOCIAL STRESS

D. Beis[1], N. Heimgartner[2], R. von Känel[3,4], C. Zuccarella-Hackl[1,5], U. Ehlert[2], P. H. Wirtz[1]

[1]Department of Psychology, University of Konstanz, Konstanz, Germany; [2]Department of Clinical Psychology and Psychotherapy, University of Zurich, Zurich, Switzerland; [3]Department of Clinical Research, University of Bern, Bern, Switzerland; [4]Department of Clinical Psychology and Psychotherapy, University of Basel, Basel, Switzerland; [5]Biological and Health Psychology, University of Bern, Bern, Switzerland

Acute psychosocial stress (PSS) activates the sympathetic adrenomedullary system and the hypothalamus-pituitary-adrenocortical axis to prime the organism for potential fight-and-flight related injuries. However, the particular role of catecholaminergic mechanisms for acute phagocyte redistribution after PSS is still ambiguous. We analyzed blood samples from 44 healthy men before and after performing a Trier Social Stress Test (TSST) concerning blood count and catecholamine changes. PSS led to increased levels of norepinephrine and epinephrine, as well as to transient granulocytosis and monocytosis immediately after the PSS. However, linear regression only linked norepinephrine increases to neutrophil changes. Most studies focus on beta adrenergic receptors (ADRs), but neglect a potential involvement of alpha ADRs in immune cell redistribution. Therefore we challenged 21 men with a Latin-square infusion protocol to mimic the duration and range of plasma norepinephrine changes during the TSST (with or without previous alpha ADR blocker administration) in comparison to a saline only condition. Our results indicate a role of alpha ADR activation by norepinephrine for the acute redistribution of neutrophils and monocytes.

OP23 EFFECTS OF PRIOR CHRONIC PSYCHOSOCIAL STRESS ON SUBSEQUENT BLUNT THORAX TRAUMA IN MALE MICE

D. Langgartner[1], A. Palmer[2], S. O. Reber[1] , M. Huber-Lang[2]

[1]Laboratory for Molecular Psychosomatics, Clinic for Psychosomatic Medicine and Psychotherapy, University of Ulm, 89081 Ulm, Germany, [2]Department of Traumatology, Hand-, Plastic-, and Reconstructive Surgery, Center of Surgery, Medical School University of Ulm, Ulm, Germany

An overshooting local or systemic inflammation during the early phase following blunt thorax trauma (TXT) promotes the development of acute lung injury, acute respiratory distress syndrome, or even multiple organ failure, as well as subsequent mortality. Given that individuals diagnosed with a life history of psychosocial stress/ trauma are characterized by chronic low-grade inflammation, we hypothesize that "psychosocial preload" poses a risk factor for the above mentioned complications following TXT. To test our hypothesis, we employed the chronic subordinate colony housing (CSC) paradigm to induce "psychosocial preload" and systemic low-grade immune activation in male mice. Subsequent, anesthetized CSC and respective single-housed control (SHC) mice were exposed to TXT, induced by a single blast wave centered on the thorax, or to SHAM treatment (anesthesia only). All mice were euthanized either 2h, 6h, or 24h after TXT or SHAM. To assess the effects of psychosocial stressor exposure on the immunological consequences of subsequent TXT, we currently analyze bronchioalveolar lavage (BAL) cytokine- and total protein concentrations, BAL cell counts and plasma cytokine levels in all groups and at all time points. Furthermore, to ensure that the CSC model reliably worked, we analyze adrenal and spleen weight, basal and lipopolysaccharide-induced spleen cell viability and glucocorticoid resistance, as well as plasma cytokine levels. So far, our data indicate that chronic psychosocial stress during adulthood slightly aggravates TXT-induced local immune responses, but overall has to be considered as rather negligible risk factor in terms of associated complications caused by TXT as monotrauma.

OP24 EFFECTS OF REPEATED MIXING AND SOCIAL STATUS ON BEHAVIOURAL, ENDOCRINE AND IMMUNE RESPONSES OF GROUP-HOUSED PREGNANT SOWS (*SUS SCROFA*)

C. Schalk, B. Pfaffinger, S. Schmucker, V. Stefanski

Behavioral Physiology of Livestock, University of Hohenheim, Stuttgart, Germany

Housing gestating sows in social groups is mandatory for welfare reasons. This often imposes mixing of sows and may lead to an increase of aggressive interactions, which is known to alter immune cell numbers due to an activation of stress systems. Therefore, the present study investigated the effects of repeated social mixing and rank position on aggressive behaviour, stress hormones and leukocyte subsets of sows during gestation. Pregnant sows (n=40) were housed in groups of 5 animals each and were assigned either to a social mixing treatment (MT) with an interchange of 2x2 sows between groups twice a week or remained undisturbed in their original composition (NON-MT). Blood samples (n=5) were collected and distribution of

leukocyte subpopulations as well as plasma cortisol concentrations were analysed. Although there was a gradual decline in aggressive behaviour after the first regroupings, MT sows always maintained higher levels of aggression compared to NON-MT sows. A clear rank dependency for aggressive behaviour was observed. In all sows pregnancy related alterations were seen, but a more pronounced decrease of T cells and T cell subsets was evident in MT sows. Middle ranking sows showed a stronger increase in cortisol, but no influence of treatment was found. Although our results indicate that the individual rank position influences the HPA-axis in pregnant sows, cortisol was not affected by treatment. However, repeated social mixing seems to have an effect on immune cell numbers, which has been previously reported under stressful conditions and may adversely affect sows' health and welfare.

OP25 BEHAVIORALLY CONDITIONED IMMUNOSUPPRESSION REDUCES INFLAMMATORY RESPONSES AND CLINICAL SYMPTOMS IN A MODEL OF RHEUMATOID ARTHRITIS IN RATS

L. Lückemann[1], M. Hadamitzky[1], E. M. Martinez-Gomez[1], M. Unteroberdörster[3], C. Wolff[2], H. Stangl[2], H. Engler[1], R. Straub[2] and M. Schedlowski[1]

[1]Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, 45122, Essen, Germany; [2]Lab NeuroEndocrinoImmunology Department of Internal Medicine I, University Hospital of Regensburg, 93053, Regensburg, Germany; [3]Department of Neurosurgery, University, Hospital Essen, University of Duisburg-Essen, 45122 Essen, Germany

In an established paradigm of taste-immune conditioning in rats, the novel taste saccharine (conditioned stimulus/CS) is combined with an i.p. injection of the immunosuppressive drug cyclosporine A (CsA; unconditioned stimulus/US). With this paradigm we analyzed in two experimental settings the effects of learned immunosuppression on disease progression in a model of chronic inflammatory autoimmune disease (collagen type II-induced arthritis) in rats. In both experiments, rats were behaviorally conditioned with three CS/US pairings, starting nine days prior to induction of arthritis. Retrieval to the CS at day 14 after arthritis immunization significantly reduced the inflammatory response and diminished clinical symptoms of arthritis. In contrast, when retrieval started one day after disease induction and before the emergence of the first arthritis symptoms, learned immunosuppression significantly reduced clinical symptoms only in the acute phase, however, not in the chronic phase of the disease. These results indicated that learned immunosuppression might be beneficial in the treatment of chronic inflammatory autoimmune diseases by diminishing disease exacerbation.

OP26 IMPACT OF PSYCHOLOGICAL FACTORS ON PHYSICAL ACTIVITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

L. Lipovskiy, C. G. O. Baerwald, O. Seifert

Rheumatology Unit, University Hospital Leipzig, Germany

Statement of Purpose: Physical activity in patients with rheumatologic diseases is a recommended part of the therapy. **Objective:** To characterize physical activity some psychologic factors were studied together with clinical and laboratory parameters in patients with systemic Lupus erythematosus (SLE). **Methods**: International Physical Activity Questionnaire (IPAQ-LF), the Metabolic Equivalent of Task (MET)-minutes per week (min/wk), Beck Depression Inventory (BDI-II), pain scores (VAS, PainDETECT), quality of life questionnaire (SF-36) and disability (Health Assessment Questionnaire, HAQ-DI) as well as patients self-reported reasons "not to be physically active" were used in 85 SLE patients with Disease Activity Index (SLEDAI) 4,95 ± 2,8. **Results:** 42,4 % of SLE patients were physically inactive (525,2 ± 277,3 MET-Min/wk) or moderate active (2448 ± 932,4 MET-min/wk). Deficiency in physical activity was associated with higher depressiveness ($p = 0,04$) and lower quality of life ($p < 0,05$). In contrast, the SLEDAI was not associated with the levels of physical activity. Interestingly, SLE patients indicated the following disease-related symptoms as the reason for the lower physical activity: «lupus flare» (42,5 %), as well as «fatigue» (27,6%). **Conclusion**: Deficiency in physical activity is associated with psychological factors in SLE patients. Clinicians may consider routinely monitoring and assessing the psychological well-being in SLE patients and educate them about the potential benefits of physical activity in improving their health.

OP27 DIURNAL RHYTHMS OF BLOOD LEUKOCYTES DIFFER BETWEEN LONG DAY AND SHORT DAY CONDITIONS IN DOMESTIC PIGS

L. C. Engert, U. Weiler, B. Pfaffinger, V. Stefanski, S. S. Schmucker
Behavioral Physiology of Livestock, University of Hohenheim, Stuttgart, Germany

Diurnal and seasonal rhythms influence physiology, behavior, and also the immune system of mammals, leading to, e.g., diurnal changes in blood leukocyte numbers. Thereby, seasonal differences are mainly controlled by the length of the photoperiod with short day conditions (SD) during winter and long day conditions (LD) during summer. While the photoperiod is already described to influence porcine reproduction and growth, its effect on the porcine immune system is not well known yet. Thus, we investigated whether diurnal rhythms of blood leukocytes differ between SD and LD in pigs. Castrated male pigs were held under SD (8 h light) or LD (16 h light), were fed concentrate twice daily, and had *ad libitum* access to hay and water. Blood samples were taken via indwelling vein catheters every 2 h over 50 h-periods. Leukocyte subsets were characterized by flow cytometry. Additionally, plasma cortisol concentration and activity behavior of the pigs were analyzed. Cosinor analyses revealed that the relative amplitudes of T cell, NK cell, and monocyte counts in blood were higher under SD than under LD as was physical activity. T cell, NK cell, dendritic cell, and eosinophil numbers in blood as well as physical activity and plasma cortisol concentration peaked earlier in relation to the time of lights on under SD than under LD. Decreasing immune cell numbers in porcine blood were mainly associated with increasing cortisol concentration and physical activity. In conclusion, the

photoperiod influences diurnal rhythms in the porcine immune system, accompanied by differences in endocrinology and behavior.

OP28 SLEEP ENHANCES NUMBERS AND FUNCTION OF MONOCYTES AND IMPROVES BACTERIAL INFECTION OUTCOME IN MICE

J. Hahn[1], M. Günter[1], K. Bieber[1], T. Lange[2], S. E. Autenrieth[1]

[1]Department of Internal Medicine II, University of Tübingen, 72076 Tübingen, Germany; [2]Clinic for Rheumatology, University of Lübeck, 23562 Lübeck,

Sleep has a strong impact on both humoral and cellular immunity, but its acute effects on innate immune defense against pathogens remain unclear. Here we elucidated in mice whether sleep affects innate immune cells and defense against systemic bacterial infection. Mice were allowed to sleep for 6 hours at the beginning of the resting phase and compared to mice kept awake for the same time. Sleep significantly increased the frequency and absolute cell counts of classical and non-classical monocytes in blood and secondary lymphatic organs whereas neutrophils (PMNs) were unaffected. Sleep-induced changes in monocyte numbers did not involve CCR2 signaling and were not caused by alterations in myelopoiesis, bone marrow egress or cell death, redistribution to peripheral tissues or differentiation into macrophages. On the contrary, sleep also enhanced monocyte content in lung and gut as well as macrophage numbers in spleen. These findings suggest that sleep reduced monocyte adhesion in the marginal pool and promoted monocyte extravasation to peripheral tissues. Moreover, sleep enhanced the antimicrobial activity of monocytes and PMNs as shown by increased production of reactive oxygen species by these cells. In a mouse model of systemic bacterial infection to mimic sepsis, the bacterial load in the spleen of 'sleeping' mice was profoundly reduced throughout the infection. Consequently, sleep significantly increased survival upon infection. These data provide first evidence that sleep enhances numbers and function of innate immune cells and supports early defense against bacterial pathogens.

OP29 LEARNED T CELL SUPPRESSION IN RENAL TRANSPLANTED PATIENTS

J. Kirchhof, L. Petrakova[1], J. Laubrock[1], J. Müller[1], A.Brinkhoff[2], B.Wilde[2], O.Witzke[2], M.Schedlowski[1]

[1]Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, [2]Nephrology Department, University Hospital Essen

It is well documented that immune functions can be modulated by behavioral conditioning. A possible clinical application of a conditioning paradigm is the combination with the pharmacological immunosuppressive regimen, aiming at reduction of drug dosages, thereby minimizing unwanted drug effects while maximizing therapeutic benefit for the patients. We established a conditioning paradigm with renal transplanted patients who take the immunosuppressive drug Cyclosporin A (CsA) or Tacrolimus (Tac) twice a day. After the assessment of a baseline kinetic of the T_H1 cytokine levels and T cell proliferation 2, 6 and 10 h

after the first drug intake on day 1, patients combined their medication (unconditioned stimulus, US) with a novel tasting drink serving as the conditioned stimulus (CS) twice a day on day 2, 3 and 4. During evocation on day 7 and 8, two additionally placebo intakes were included 4 h and 8 h after the drug intake together with the CS. On day 8, immunological parameters were analyzed again and compared to baseline kinetic. Results demonstrate that the conditioning process prevented the circadian attenuation of the immunosuppressive effect causing significantly lower T_H1 cytokine levels and $CD4^+$ T cell proliferation when compared to the pharmacological treatment only. These data demonstrate a "proof of principle" for the efficacy of systematically implementing conditioning process into routine immunosuppressive pharmacological regimen.

OP30 INFLAMMATORY MONOCYTE GENE EXPRESSION IN MAJOR DEPRESSIVE DISORDER

L. Grosse[1], V. Arolt[1], H. A. Drexhage[2]

[1]Department of Psychiatry, University of Münster, Germany; [2]Department of Immunology, Erasmus Medical Center (EMC), Rotterdam, The Netherlands.

At least for a subgroup of patients, inflammatory processes appear to play an important role in the development of major depressive disorder (MDD). In circulating monocytes of individuals with mood disorders, aberrant expressions of immune genes have been observed previously. However, no systematic investigation was conducted in MDD yet. We aimed at investigating a) whether MDD is associated with increased inflammatory monocyte activation, b) whether monocyte activation is particularly increased in subgroups of MDD, and c) whether monocyte activation could predict non-response to antidepressants. Two independent case-control samples were studied in a cross-sectional and in a prospective study design before and after treatment. Isolated $CD14^+$ monocytes' gene expression levels were determined using quantitative real-time polymerase chain reaction (qPCR). Circulating monocytes' expression of inflammatory and immune genes a) was not uniformly raised in different MDD samples, but b) particularly occurred in clinically relevant subgroups of MDD, e.g. in patients who were drug-free and severely depressed, in MDD patients aged above a certain age (≥ 28 years), and in MDD patients with an insufficient response to antidepressants. In the two MDD samples studied, increased inflammatory gene expression was paralleled by a reduced gene expression of the active glucocorticoid receptor (GR) GRα isoform versus the expression of the inactive isoform GRβ. Taken together, the present data strengthen the view that altered immune processes play a significant role in subgroups of depression. The new method of monocyte gene expression analysis led to the identification of patient subgroups with high clinical significance.

OP31 DISTURBED AFFECTIVE COGNITION DURING EXPERIMENTAL ENDOTOXEMIA

S. Benson[1], A. Brinkhoff[1,2], L. Lueg[1], H. Engler[1], M. Schedlowski[1], S. Elsenbruch[1]

[1]Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen; [2]Department of Nephrology, University Hospital Essen

Systemic inflammation is increasingly recognized as risk factor for depression. Disturbances of affective cognition have been observed after experimental induction of sad mood, but also constitute a core aspect of depression. Herein, we combined human experimental endotoxemia as a model to induce a transient systemic immune activation with an established experimental mood induction procedure to assess the effects on an affective Go/Nogo task as measure of affective cognition. In this randomized cross-over study, N=15 healthy males received either 0.8ng/kg LPS or placebo on two otherwise identical study days. The affective Go/Nogo task was conducted after experimental induction of neutral and sad mood on both study days. Low-dose LPS induced significant increases in leukocyte counts, interleukin-6, and body temperature (all $p<.01$, interaction effects). Mood induction led to greater sadness ratings, with highest ratings when sad mood was induced during systemic inflammation ($p<.05$, interaction effect). Based on a 2 (LPS vs. placebo) x 2 (sad vs. neutral mood) x 2 (sad vs. happy Go/Nogo target words) factorial design, we observed a significant target x LPS condition interaction ($p<.01$). This reflects that subjects responded slower to sad (compared to happy targets) during endotoxemia. Additionally, we found a valence x mood interaction ($p<.05$), reflecting slower reaction times to sad words in sad mood. Together, our data support that inflammation and sad mood are risk factors for disturbed affective cognition. The results may reflect a so called mood-congruency effect, which proposes prolonged and sustained processing of mood-congruent information in depressed individuals.

OP32 EXPECTATIONS SHAPE THE EMOTIONAL RESPONSE OF EXPERIMENTALLY-INDUCED SICKNESS

J. Lasselin[1,2.3], P. Petrovic[2,4], M. J Olsson[2], S. Paues-Göranson[5], M. Lekander[2,3,4], J. Axelsson[2,3,4], K. Jensen[2,4]

[1]Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, Hufelandstr. 55, 45 122 Essen, Germany; [2]Department of Clinical Neuroscience, Division for Psychology, Karolinska Institutet, Nobels väg 9, 171 65 Solna, Stockholm, Sweden; [3]Stress Research Institute, Stockholm University, Frescati Hagväg 16A, 106 91 Stockholm, Sweden; [4]Osher Center for Integrative Medicine, Karolinska Institutet, Scheeles väg 1, 171 65 Solna, Stockholm, Sweden; [5]Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, 171 77 Stockholm, Sweden

Experimentally-induced sickness (EIS) is a well-established model to assess the neuropsychiatric effects of inflammation. Although high inter-subject variability exists in EIS response, predictors are scarcely studied. The aim of this study was to assess the effect of expectations on EIS outcomes, using a Bayesian predictive coding perspective. In a placebo-controlled crossover design, 22 healthy volunteers were injected with lipopolysaccharide (LPS), which activates the immune system. Expectancy of treatment effect was assessed using a numerical scale based on previous experience of sickness (e.g., “I think that today I will feel much worse than usually when I am sick”). Interleukin-6 (IL-6) plasma concentration was used as an index of the input

(immune) signal magnitude. Treatment effect was assessed by measuring sickness symptoms. State anxiety and positive affect/arousal were measured to evaluate emotional responses. LPS resulted in increased IL-6 concentrations, sickness symptoms and state anxiety, while positive affect and arousal decreased. After LPS, the immune signal (IL-6 concentrations) predicted stronger sickness symptoms, higher state anxiety and more negative arousal. Negative expectations of LPS were associated with less adverse emotional outcomes. The "error signal", defined as the discrepancy between the immune signal and expectation of the treatment effect, was a significant predictor of negative emotional outcomes after LPS. These findings indicate that when low expectations of becoming sick are met with a strong immune activation, it results in a strong error signal and more negative emotional response. We propose that knowledge of expectations are important to understanding inflammation-induced neuropsychiatric symptoms.

OP33 METABOLITE FINGERPRINTING REVEALS NEW SERUM METABOLITES AND ASSOCIATED PATHWAYS IN POSTTRAUMATIC STRESS DISORDERS

A. Karabatsiakis[1], W. Wilker[1], G. Hamuni[1], S. Kolassa[2],D. Renu[3], S. Kadereit[4], M. Schauer[5], T. Hennessy[6], I.-T. Kolassa[1]

[1]Clinical & Biological Psychology, Institute of Psychology & Education, Ulm University, Ulm, Germany. [2]SAP Switzerland AG, Tägerwilen, Switzerland.[3]Strand Life Sciences Pvt. Ltd., Bangalore, India. [4]Department of Life Sciences Albstadt-Sigmaringen University of Applied Sciences, Sigmaringen, Germany. [5]Clinical Psychology, Kompetenzzentrum Psycho-traumatologie, University of Konstanz, Konstanz, Germany. [6]Agilent Technologies Pty Ltd, Brisbane, Australia.

Background: Posttraumatic stress disorder (PTSD) is associated with an increased risk for adverse physical health outcomes. However, the underlying biomolecular processes and associated pathways remain poorly elucidated. The metabolome includes all hydrophilic and amphiphilic metabolites. Using time-of-flight mass spectrometry (qTOF-MS), the untargeted and holistic investigation of the metabolome holds the potential to provide novel insights into PTSD pathophysiology and might further help to understand the interplay between the endocrine, the immune and the central nervous system. *Method:* Serum from 20 individuals with PTSD diagnosis and 18 healthy controls was analyzed using qTOF-MS. Groups were matched based on age and ethnicity. Symptom severity of PTSD was assessed using the Clinician-administered PTSD scale (CAPS). Univariate and multivariate approaches, namely *Partial Least Square Discriminant Analysis* (PLS-DA), were applied for statistical analyses. *Results:* The group comparison revealed 13 metabolites significantly altered in PTSD, including four glycerophospholipids and one metabolite involved in endocannabinoid signaling. Out of the 13, eleven metabolites showed a correlation between the serum level and the CAPS score. In the multivariate approach, a metabolite profile of 19 biomolecules predicted PTSD with an accuracy of 85%. *Conclusions:* Here, we illustrate the potential of metabolite fingerprinting to identify

novel pathophysiological underpinnings of PTSD. It further provides the possibility to highlight associated pathways, such as lipid-derived and endocannabinoid signaling in PTSD. More research is needed to gain a deeper understanding of the molecular mechanisms and associated pathways not only of the disease per se, but also of the biological processes stimulated by (psycho)therapeutic treatment.

OP34 INFLAMMATION AND THE BRAIN IN MALTREATMENT AND DEPRESSION: A NEUROIMAGING PERSPECTIVE

R. Redlich, U. Dannlowski

Department of Psychiatry, University of Muenster, Germany

Major depressive disorder (MDD) is one of the most debilitating diseases worldwide. Since effective treatment and prevention require knowledge of risk factors and their neurobiological mechanisms, there is a need for more detailed understanding of the neurobiological implications. Emerging evidence suggests that MDD entails extensive alterations in brain structure, -function and the inflammatory system. However, it is still unknown whether these inflammatory and neurobiological alterations represent a consequence or a predisposition of depression. Childhood maltreatment is a leading risk factor for mental illness. Although the association between maltreatment and depression has been extensively proven, there is an urgent need to understand how maltreatment increases the risk of depression. In the last decade, there has been increasing focus on the role of inflammation and its crosstalk with neurocircuits as a potential mechanism to bridge this gap. There is rising evidence that early-life stress could act through both the modulation of inflammatory responses and the neurobiological alterations up to adulthood or over the lifespan. Genetics, inflammatory and neurobiological alterations comprise the mechanisms that are most likely to increase the vulnerability of developing depression.

OP35 STRONG AGE-DEPENDENT EFFECTS OF DOPAMINE ON THE AGGRESSIVE FIBROBLAST PHENOTYPE IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS PATIENTS

L. van Nie[1], S. Rehart[2], E. Neumann[1], U. Müller-Ladner[1], S. Capellino[3]

[1]Department of Internal Medicine and Rheumatology, Justus-Liebig-University Gießen, Kerckhoff-Klinik, Bad Nauheim [2]Department of Orthopedics and Trauma Surgery, Apaglesion Markus Hospital, Frankfurt am Main. [3]Dept. of Immunology, Leibniz Research Centre for Working Environment and Human Factors, Dortmund. Germany

Objectives: Preventing migration of synovial fibroblasts (SF) into the adjacent cartilage is a desirable therapeutic target in rheumatoid arthritis (RA), especially in order to avoid joint destruction. Previous studies suggest an involvement of the dopamine pathway in RASF. Aim of this study was therefore to investigate dopamine-mediated effects on joint invasion and destruction in RA. *Materials and Methods:* RA and osteoarthritis (OA) SF were obtained from patients undergoing knee joint replacement surgery. Distribution of the five dopamine

receptors (DR) was evaluated via immunohistochemistry in the synovium, with special focus on the lining layer and the invasion zone. After stimulation of D1-like and D2-like DR, SF migration and motility were evaluated. *Results:* D1DR, D4DR and D5DR were found to be expressed more intensely close to the invasion zone as compared to the sublining layers. Migration of RASF and OASF was highly correlated with the patients' age at surgery. While younger patients (≤ 75years) showed an increase in migration up to 78%, older patients (≥ 75years) showed a reduced migration of up to 50% (OA n=8; RA n=7). We observed no difference between RA and OA patients and between D1-like and D2-like receptor stimulation. The same effect could be described in the motility assay (OA n=5; RA n=6). *Conclusion*: Taken together, our results suggest a direct role of dopamine on the aggressive phenotype of fibroblasts in arthritis. Therefore, synovial dopamine pathway appears to be a potential therapeutic target of RA.

OP36 IDENTIFICATION OF ANTI-INFLAMMATORY EFFECTS OF OXYTOCIN IN ENDOTOXEMIC MALE RATS BY HEART RATE VARIABILITY ANALYSIS

J. Reyes-Lagos[1,2], A. R. Elorza-Ávila[2], M. Hadamitzky[3], M. Ángel Peña-Castillo[1], J. C. Echeverría[1], M. Rocío Ortiz-Pedroza[1], L. Lückemann[3], M. Schedlowski[3], Gustavo Pacheco-López[4]

[1]Metropolitan Autonomous University (UAM) Iztapalapa campus, Mexico. [2]Autonomous University of the State of Mexico (UAEMex), Mexico. [3]University Hospital Essen, Germany. [4]UAM Lerma campus, Mexico.

Cardiac rhythm shows a complex dynamics, due to non-linear interaction between cardiac pacemaker cells and the autonomic nervous system (ANS). Analysis of heart rate variability (HRV) is a noninvasive ANS assessment method. HRV provided evidence to show that heart rate dynamics are altered during systemic inflammation. The neuropeptide oxytocin (Ox) has anti-inflammatory and cardioprotective roles and improves vascular and metabolic function. We documented that peripheral lipopolysaccharide (LPS) administration induces cytokine-induced sickness behavior. The aim for this study was to explore the potential anti-inflammatory effects of Ox by linear- and nonlinear- HRV measures and other electrocardiogram derived measures in freely moving rats. In a between-subjects experimental design, animals received peripheral treatments: vehicle (V); LPS; Ox; LPS+Ox. We found that the non-linear scaling parameter α1(SIGN) identifies the LPS-induced inflammatory process. The LPS injection produced anticorrelated (lower) values in this parameter in comparison to control (V vs. LPS), but in contrast the LPS injection combined with Ox produced a less anticorrelated (higher) values in the endotoxemic rats (LPS vs. LPS+Ox). Ox increased the natural logarithm of the high frequency parameter, related to the vagal activity (LPS vs. LPS+Ox). Also, Ox administration attenuated the hyperventilation and taquichardia produced by the LPS-induced endotoxemia (LPS vs. LPS+Ox). Finally, the anti-lethargic and long-term temperature moderating effects of Ox administration during endotoxemia could be a consequence of the systemic anti-inflammatory properties of Ox. Our recent results support evidence that Ox may act as an anti-inflammatory agent, possibly modulating the cholinergic anti-inflammatory pathway in the cardiorespiratory system.

OP37 THE NEUROPEPTIDE ALPHA-MSH COUNTERACTS UVA-INDUCED OXIDATIVE STRESS IN DERMAL FIBROBLASTS VIA REGULATION OF CATALASE

M. Böhm[1], A. Stegemann[1], A. Mastrofrancesco[2], M. Picardo M[2], E. Healy[3]

[1]Dept. of Dermatology, University of Münster, Germany; [2]San Gallicano Dermatological Institute, Rome, Italy; [3]Dermatopharmacology, University of Southampton, Southampton General Hospital, Southampton, UK

Irradiation with ultraviolet A (UVA) is a key pathogenetic factor in dermal photoaging. Notably, individuals with loss of function (LOF) mutations in the melanocortin-1 receptor (MC1R) display increased signs of dermal photoaging. Thus, MC1R and its physiological ligand, the neuropeptide alpha-melanocyte-stimulating hormone (alpha-MSH), may regulate oxidative stress in human dermal fibroblasts (HDFs) exposed to UVA. Here, we show that alpha-MSH suppresses UVA-mediated accumulation of oxidative stress, i. e. H_2O_2, in HDFs in a cAMP-dependent manner. Consistent with this, mouse 3T3 fibroblasts stably expressing MC1R displayed reduced oxidative stress upon UVA exposure. Agouti signalling protein, a natural MC1R antagonist, blocked the protective effect of alpha-MSH in HDFs exposed to UVA. HDFs carrying LOF mutations of *MC1R* displayed increased basal levels of H_2O_2 and failed to respond to alpha-MSH. Importantly, the protective effect of alpha-MSH on UVA-induced oxidative stress was paralleled by reduced mRNA expression and secretion of both MMP1 and MMP3, key enzymes in dermal photoaging. Mechanistically, alpha-MSH upregulated activity of catalase but not mRNA and protein expression of this enzyme in HDFs. Gene knock-down of catalase abrogated the suppressive effect of alpha-MSH on UVA-mediated accumulation of H_2O_2. These findings identify the MC1R-alpha-MSH axis in HDFs as a novel photoprotective pathway in cutaneous photobiology.

OP38 NOVEL NEUROENDOCRINE PERSPECTIVES IN HUMAN MELANOCYTE BIOLOGY: VASOACTIVE INTESTINAL PEPTIDE (VIP) REGULATES HUMAN HAIR FOLLICLE PIGMENTATION

M. Bertolini[1,2], M. Bähr[3], M. Sulk[1], L. Ponce[2], J. Hardmann[4], T. Bíró[5], D. Tobin[6], R. Paus[4]

[1]Dept. of Dermatology, University of Münster, Münster, Germany; [2]Monasterium Laboratory, Münster, Germany; [3]Medical School, University of Lübeck, Lübeck, Germany; [4]Centre for Dermatology Research, Institute of Inflammation and Repair, University of Manchester, Manchester, UK; [5]Dept. of Immunology, University of Debrecen, Debrecen, Hungary; [6]Centre for Skin Sciences, University of Bradford, Bradford, UK.

Exploratory pilot experiments in our lab had raised the possibility that vasoactive intestinal peptide (VIP), a key immunoinhibitory neuropeptide released by perifollicular sensory nerve fibers, may be a novel modulator of human HF pigmentation. This hypothesis was followed-up in the current study by investigating whether VIP (10^{-7}M) modulates human HF pigmentation *in situ* and in isolated human HF melanocytes (HFiMc). VIP significantly increased both, the number of intraepithelial c-Kit+ HF melanocytes (HFMc) *in situ* and intrafollicular c-Kit transcription. Instead, VIP down-regulated SCF gene and protein expression in organ-cultured human HFs. Interestingly, c-Kit/gp100 double- immunostaining indicated that most of the VIP-

induced, c-Kit+ HFMc represent immature/amelanotic HFMc. Intriguingly, VIP up-regulated the total number of gp100+, MITF+, or p-MITF+ HFMc and promoted intrafollicular melanin production *in situ*. VIP also significantly stimulated melanogenesis in isolated human HFiMc, suggesting that it impacts directly on HFMc, but slightly inhibited HFMc/HFiMc proliferation *in situ* and *in vitro*. Preliminary results obtained with specific antagonists suggested that VPAC1 and VPAC2 mediated the VIP effects on HFMc. Since microarray and qRT-PCR analyses showed an up-regulation of phosphodiesterase 4D7 transcription in VIP-treated HFs, VIP may regulate the cAMP level in HFMc, possibly by utilizing downstream pathways shared with α–MSH signaling. In summary, our results reveal VIP as a novel, surprisingly complex and clinically relevant neuroendocrine regulator of human HF pigmentation.

OP39 ALPHA-MSH ACTIVATES MELANOCORTIN 4 RECEPTOR IN IMMUNE COMPLEXES WITH ALPHA-MSH-REACTIVE PLASMATIC IgG - NEW NEUROIMMUNE MECHANISM OF PEPTIDE SIGNALING ALTERED IN OBESITY AND EATING DISORDERS

N. Lucas[1], R. Legrand[1], C. Bôle-Feysot[1], J. Breton[1], M. Coëffier[1], K. Akkermann[2], A. Järv[3], J. Harro[2], P. Déchelotte[1], S. O. Fetissov[1]

[1]Inserm UMR1073, Nutrition, Gut and Brain Laboratory, University of Rouen Normandy, Rouen, France; [2]Department of Psychology and [3]Psychiatric Hospital, University of Tartu, Tartu, Estonia.

Activation of the melanocortin 4 receptor (MC4R) by alpha-melanocyte-stimulating hormone (α-MSH) induces satiety, while MC4R deficiency leads to hyperphagia and obesity. We have previously shown the ubiquitous presence of plasmatic α-MSH-reactive immunoglobulins (Ig) which levels correlate with behavioral traits in humans and rodents. The functional role of α-MSH-reactive IgG in MC4R signaling remained, however, unknown. Here we show that human α-MSH-reactive IgG bind in vitro and activate MC4R expressing cells only as immune complexes together α-MSH. Further, α-MSH-reactive IgG from plasma of obese and eating disorder patients display altered kinetics of α-MSH immune complex formation and reduced MC4R affinity found in obesity. Remarkably, α-MSH/IgG immune complex with IgG from all, except obese subjects, display lower MC4R-mediated cAMP activation threshold as compared with the α-MSH peptide alone. Furthermore, MC4R-linked cell internalization of α-MSH/IgG immune complex was decreased in obese and increased in anorectic patients. These data suggest that in circulation α-MSH binds and activates MC4R not as a single peptide molecule but as an immune complex with IgG and that different binding properties of α-MSH-reactive IgG may underlie altered MC4R signaling in obesity and eating disorders.

OP40 ALPHA-MELANOCYTE-STIMULATING HORMONE CONTROLS SKIN CARCINOGENESIS BY INHIBITING THE EXPANSION OF MYELOID-DERIVED SUPPRESSOR CELLS IN A TLR4-DEPENDENT MANNER

N. Mykicki[1], C. Weishaupt[1], T. Vogl[2], J. Roth[2], T.A. Luger[1], K. Loser[1]

[1]Department of Dermatology and [2]Institute of Immunology, University of Münster, 48149 Münster, Germany

The neuropeptide alpha-melanocyte-stimulating hormone (α-MSH) is a potent immunomodulatory and since the development of skin cancer is controlled by the immune system we investigated the effects of α-MSH on skin carcinogenesis. In a two-stage chemo-carcinogenesis study α-MSH-treated mice developed significantly fewer skin tumors compared to controls. However, the total numbers of CD8+ T-cells expressing cytolytic markers like perforin, granzymes, FasL or Eomes were significantly increased in tumor tissue and tumor-draining lymph nodes from α-MSH-treated mice. Next, we analyzed the underlying cellular mechanism and could demonstrate that α-MSH prevented the expansion of myeloid-derived suppressor cells (MDSC), which are known to inhibit MHC class-I-restricted anti-tumoral immunity. Since it has been shown that ligation of TLR4 by the damage-associated molecular pattern (DAMP) proteins S100A8/A9 and the subsequent activation of NF-κB is essential for MDCS generation we analyzed NF-κB activation and TLR4 signaling. Interestingly, compared to controls, tumors from α-MSH treated mice were characterized by decreased levels of S100A8/A9 as well as a reduced expression of CD14 and IRAK-1, both signaling proteins downstream of TLR4. To further elucidate the role of α-MSH in inhibiting S100/TLR4 signaling and thus, the expansion of MDSC we performed a two stage skin carcinogenesis in mice deficient for S100A8/A9. Strikingly, α-MSH did neither reduce tumor development nor prevent the expansion of MDSC in these animals. Together, our data demonstrate that α-MSH down-regulated the DAMP proteins S100A8/A9 resulting in the inhibition of TLR4 signaling and NF-κB activation, finally leading to the suppression of MDSC expansion and the up-regulation of tumor-specific CTL.

Poster presentations

PP01 FLUORESCENCE-BASED NEUROTRANSMITTER RECEPTOR MONITORING ON B-CELLS

K. Krebber, T. Lowin, M. Schneider, G. Pongratz

Dept. of Rheumatology & Hiller Research Center for Rheumatology, University Hospital Düsseldorf

Background: Splenic B-cells isolated from immunized DBA mice, show increased IL-10 upon β2-adrenergic stimulation and diminish collagen-type II induced arthritis after transfer. Naive B-cells do not show this responsiveness. Change of responsiveness to neurotransmitters might be due to change of neurotransmitter receptor patterns on B-cells. **Objective:** Development of a fluorescence based method to detect changes in expression patterns of neurotransmitter receptors on B-cells. **Methods:** Detection of receptors on magnetically sorted murine B-cells with fluorescent ligands (A-633-AG, BODIPY-FL-Prazosin, S-Propranolol-red) by flow cytometry.

Dislocation of fluorescent ligands through unlabeled ligands to show specificity of binding. **Results and conclusions:** Naive murine B-cells showed binding of fluorescent BODIPY-FL-Prazosin, an α1-adrenergic receptor (AR) agonist, which was displaced by nonfluorescent Doxazosin by 30 %. The incomplete dislocation might reflect unspecific binding, membrane translocation, or internalization of receptor, which needs further investigation. Fluorescent S-Propranolol-red, a β2-AR antagonist, shows an increased fluorescence after pre-incubation with the unlabelled ligand Nadolol in comparison to fluorescence without competitor. This was unexpected and needs further investigation. The fluorescent ligand A-633-AG binds to all adenosine receptor subtypes (A1, A2A, A2B, A3) but can be displaced by subtype specific unlabeled ligands on naive B-cells. Consequently, this ligand is suitable to determine changes in adenosine receptor expression patterns. **Conclusion:** Fluorescence-based receptor monitoring is complex, mainly due to unfavorable signal to noise ratio, which needs further improvement, especially for the β2-AR subtype. However, using fluorescence-based receptor detection, we found that naive murine B-cells express α1-AR and all adenosine receptor subtypes.

PP02 THE INFLUENCE OF THE INTESTINAL MICROBIOME ON THE AFFECTIVE CONSEQUENCES OF CHRONIC PSYCHOSOCIAL STRESS

J. Kunze, D. Langgartner, S. O. Reber

Laboratory for Molecular Psychosomatics, Clinic for Psychosomatic Medicine and Psychotherapy, University of Ulm, 89081 Ulm, Germany

Chronic psychosocial stress is an acknowledged risk factor for the development of affective disorders in humans. Given that chronic stress in mice has been shown to alter the microbial composition of the gut, and that changes in the intestinal microbiome are able to influence the behavior of mice, a causal role of the gut microbiome in the development of stress-induced affective disorders is very likely. A promising model to investigate this hypothesis is the chronic subordinate colony housing (CSC, 19 days) model, a pre-clinically validated mouse model for chronic psychosocial stress known to alter the microbial signature of the gut as well as to induce anxiety-related behavior. Here, we test the hypothesis that CSC-induced affective and physiological alterations can be prevented by repeated transplantation of feces from non-stressed single-housed control (SHC) mice during CSC exposure. To investigate this, we infused both SHC and CSC mice twice rectally with SHC donor feces at days 4 and 11 of the CSC paradigm. At the end of CSC, anxiety-related behavior and typical physiological CSC parameters were assessed. To exclude general effects of the rectal infusion procedure, another set of SHC and CSC mice was injected with saline at the respective days and compared to un-injected mice. So far, our data indicate that two transplantations of a non-stressed donor microbiome is not able to prevent CSC effects on anxiety-related behavior as well as physiological alterations. We currently investigate if transplantation of a stressed microbiome is able to induce well-known CSC effects in SHC mice. **Keywords:** chronic psychosocial stress, chronic subordinate colony housing (CSC), anxiety-related behavior, microbiome, fecal transplantation

PP03 LEARNED IMMUNOSUPPRESSION: EFFECTS OF A PROLONGED POST-CONDITIONING RETENTION INTERVAL

E. M. Martínez-Gómez, L. Lückemann, M. Hadamitzky, M. Schedlowski

Institute of Medical Psychology and Behavioral Immunobiology, University Hospital of Essen, University of Duisburg Essen

In a model of behaviorally conditioned immunosuppression in rats, a novel taste (saccharin) is paired as conditioned stimulus (CS) with the immunosuppressant cyclosporine A (CsA) as the unconditioned stimulus (US). During retrieval, rats avoid drinking the saccharin (conditioned taste aversion; CTA) and concomitantly display immunosuppression reflected by reduction cytokine production. However, to apply this learning protocol in clinical conditions, it is essential to know whether the strength of conditioning depends on a particular time interval that elapses between acquisition and retrieval (retention interval). The present study analyzed the effects of delayed retrieval by comparing a short (2 d) with long (30 d) retention intervals. Analyses of peripheral immune functions (anti-CD3 stimulated IL-2, IL-17 and IFN-γ cytokine production) assessed after a 30 days retention interval show, that rats still display a significant inhibition of cytokine concentrations when re-exposed to the CS. These results demonstrate that learned immunosuppression is maintained even 30 days after the initial CS-US association.

PP04 INVOLVEMENT OF KIR6.2 CHANNELS IN IL-1β-INDUCED HYPOGLYCEMIA

C. Meyer, J. Wildmann, H. Besedovsky, A. del Rey

Research Group Immunophysiology, Inst. of Physiology and Pathophysiology, University of Marburg, Germany

The cytokine interleukin-1β (IL-1β) does not only affect the immune system but also elicits relevant neuro-endocrine responses. Among them, this cytokine can induce a marked and long-lasting, insulin-independent hypoglycaemia, which is, at least partially mediated by effects of the cytokine in the brain. Furthermore there is evidence that IL-1β can change the set-point of glucose homeostasis at central levels. However, little is known about the mechanism of this phenomenon. Kir6.2 a major subunit of the inward-rectifier ATP-sensitive potassium channel, is involved in sensing glycaemia by glucose-exited neurons in the hypothalamus. We studied the participation of this channel on IL-1β-induced hypoglycemia using Kir6.2 knockout (KO) mice as model. Contrary to the information available in the literature, we found that basal glucose levels show a larger variability in Kir6.2 KO mice than in heterozygous and wildtype animals. We also found that Kir6.2 KO mice respond to IL-1β with a significantly more pronounced hypoglycemia than wildtype counterparts. Furthermore, glucose levels of IL-1β-injected Kir6.2 KO subject to a glucose load not only return quicker to hypoglycemia, but the decrease in glucose levels attained is significantly more pronounced than in normal littermates. We conclude that the mechanism of IL-1β-induced hypoglycemia is only partially counteracted by Kir6.2 signaling. In addition, catecholaminergic and serotonergic pathways known to be involved in glucose

regulation are significantly more affected by IL-1β administration in Kir6.2 KO mice than in wild type animals. This differential effect could contribute to the more marked hypoglycemia induced by IL-1β in Kir6.2 KO mice.

PP05 MHC-SIMILARITY DETERMINES LEVEL OF AGONISTIC INTERACTIONS IN NEWLY GROUPED PIGLETS

U. Gimsa[1], A. Tuchscherer[2], B. Puppe[1]

[1]Leibniz Institute for Farm Animal Biology, Institute of Behavioral Physiology, Dummerstorf, Germany; [2]Leibniz Institute for Farm Animal Biology, Institute of Genetics and Biometry, Dummerstorf, Germany

The major histocompatibility complex (MHC) is crucial for the immune defence. It presents peptides of pathogens to T lymphocytes. The ability to detect the MHC genotype of conspecifics by olfaction is known for a number of mammals. This detection is important for choosing optimal mates. However, social recognition also plays an important role in establishing and maintaining social dominance hierarchies. Recent studies suggest that pigs can discriminate related or familiar individuals by their odour. We performed two replicates to study whether MHC-mediated olfactory components influence social behaviour. In each replicate, three male piglets (4 weeks old) were taken from each of 10 litters and randomly weaned in three groups of 10 unfamiliar piglets per group. The piglets were MHC-genotyped by sequence-specific primer-PCR. Agonistic interactions in these three groups were videotaped for 72 hours, counted with respect to MHC similarity between adversaries and divided by the number of adversaries within each group and the respective category, i.e. high or low MHC similarity. Data indicated that piglets with high MHC similarity fight less than piglets with low MHC similarity. However, the clarity of this result was somewhat impaired by the unusual aggressiveness of piglets descended from one boar. This is the first time that MHC-similarity has been shown to affect agonistic interactions in sexually immature mammals. Nevertheless, more experiments with sophisticated group designs are required in order to confirm that piglets use MHC-mediated olfactory clues for the social recognition of potential relatives.

PP06 DETECTION OF THE OLFACTORY RECEPTOR OR6V1 IN CUTANEOUS CELL TYPES *IN VITRO* AND *EX VIVO*

P. Gkogkolou[1], H. Dosoki[1], M. Apel[1], T. A. Luger[1], M. Matsui[2], M. Böhm[1]

[1]Dept. of Dermatology, University of Münster, Germany; [2]Estee Lauder, Melville, USA

Olfactory receptors (ORs) are typically expressed in the nasal epithelium where they mediate communication between environmental odorants and the nervous system. Interestingly, there is evidence that expression of these G protein-coupled receptors occurs also outside olfactory sensory neurons, e.g. in the skin pointing towards a broader function of ORs far beyond smell perception. Accordingly, we could recently show that functional OR2AT4 is expressed by human epidermal keratinocytes. A synthetic sandalwood odorant induced wound-healing processes in

human keratinocytes via OR2AT4 (Busse et al. JID 2014). Here we further investigated the expression of additional ORs in cultured human epidermal keratinocytes, epidermal melanocytes and dermal fibroblasts using RT-PCR analysis, Western immunoblotting and immunofluorescence. While OR11A1, OR5V1, OR14A2, OR5D16, OR6Y1, OR10J5 and OR1G1 were undetectable in all examined cell types, melanocytes as well as keratinocytes consistently expressed OR6V1 at the RNA level. Western immunoblotting confirmed expression of this OR in both cell types. Moreover, immunofluorescence revealed OR6V1 immunoreactivity at the cell surface and within the cytoplasm of these cell types. Importantly, OR6V1 expression was also detected by RT-PCR in skin samples from the forearm of n=10 healthy volunteers. Taken together, our studies show the presence of a novel olfactory receptor, OR6V1, in human skin. Functional studies have to clarify the role of this receptor in cutaneous physiology and pathophysiology.

PP07 RESPONSES OF CULTURED DORSAL ROOT GANGLION NEURONS TO SOMATOSENSORY AND INFLAMMATORY STIMULATION

S. Leisengang, D. Ott, R. Gerstberger, C. Rummel, J. Roth
Institute of Veterinary-Physiology and -Biochemistry, Justus Liebig University Gießen

Peripheral sensory nerve endings of thermo- and nociceptors are difficult to investigate experimentally since they are thin fibres embedded in a tough layer of skin tissue. An approach to this problem is to isolate the somata of somatosensory neurons out of the dorsal root ganglia (DRG), to keep them in primary culture, and to use them for selected experimental procedures.
The investigated neurons were grouped according to their size with diameters of about 15µm (small), 35µm (medium sized), or 55µm (large). We measured intracellular Ca^{2+}-concentrations in cultured DRG neurons stimulated with cold (rapid cooling from 37 to 25°C), menthol (TRPM8-agonist), with capsaicin (TRPV1-agonist), or with the inflammatory mediator prostaglandin E_2 (PGE_2) using the fura-2 ratio imaging technique. We detected putative cold-sensitive neurons responding to cold / menthol and nociceptors responding to capsaicin with a transient increase of intracellular Ca^{2+}. A part of the cold sensitive and nociceptive cells also responded to stimulation with PGE_2. Incubation of DRG-primary cultures with lipopolysaccharide (LPS) for 2 or 4 h caused release of cytokines into the supernatant and activation of the inflammatory transcription factor NF-IL-6 in DRG-neurons. Cultured DRG neurons can, thus, be used to study cellular responses to various physical or chemical stimuli, which might activate sensory nerve endings under *in vivo* conditions. The modulation of the response patterns of these neurons under inflammatory conditions is currently investigated.

PP08 SIGNAL DEFICIENCY OF MELANOCORTIN-1 RECEPTOR AUGMENTS EXTENT OF SKIN INFECTION INDUCED BY *S. AUREUS*

H. Dosoki, M. Apel, K. Loser, M. Böhm
Dept. of Dermatology, University of Münster, Germany

The melanocortin-1 receptor (MC1R) is crucially involved in skin melanin pigmentation in many vertebrate species. It binds neuropeptides like alpha-melanocyte-stimulating hormone with high affinity. However, the role of MC1R in cutaneous infection has not been investigated to the best of our knowledge. Here, we examined the impact of MC1R deficiency in a mouse model for cutaneous infection. MC1R signaling-deficient mice *(*Mc1r*e/e*) and control mice (C57BL/6) were intradermally infected with 107 colony forming units of *S. aureus* (strain SH100). The extent of skin infection was monitored for 6 days. Interestingly, Mc1r *e/e* mice developed larger skin lesions compared with control mice. Gram staining revealed higher bacterial amounts in lesional skin of Mc1r*e/e* mice than in control mice. In accordance with this mRNA expression of nusA and sigA, two established markers for *S.aureus,* was markedly increased in Mc1r*e/e* mice. Surprisingly, the cutaneous levels of IL-6, IL-8, IL-1β and IL-17a were significantly lower in lesional skin of MC1R signaling-deficient mice than in control mice as determined by real-time RT-PCR analysis. In addition, mRNA expression of Ly6c, Ly6G and CD11b, markers of neutrophils, and subsets of monocytes / macrophages, was decreased in Mc1r*e/e* mice compared with control mice. Using FACS analysis we quantified the number of macrophages in infected skin and found an increased number of macrophages in wild-type mice vs. Mc1r*e/e* mice. In addition, increased numbers of T regulatory cells were detected in skin lesions of wild-type mice compared with MC1R signaling-deficient mice. In sum, these findings indicate that MC1R is involved in controlling both the extent of infection and subsequent immune response of the skin to *S. aureus.*

PP09 TOPICAL APPLICATION OF WOL074-009, WOL074-019 AND WOL074-029 TRIPEPTIDES EXHIBITS STRONG ANTI-INFLAMMATORY ACTIVITY IN A MOUSE MODEL OF PSORIASIS

M. Schneeweiss[1], A.-Lena Geiselhöringer[1], C. Sternemann[1], M. Soeberdt[2], U. Knie[2], C. Abels[2], T. A. Luger[1], K. Loser[1]

[1]Department of Dermatology, University of Münster, 48149 Münster, Germany; [2]Dr. August Wolff GmbH & Co. KG -Arzneimittel, 33611 Bielefeld, Germany

The tripeptide KdPT has anti-inflammatory and immunomodulatory activities and was effective in mouse models of intestinal inflammation and psoriasis. Unfortunately, due to its unfavorable physicochemical properties KdPT cannot be developed in a topical formulation. Therefore, we designed analogues of KdPT [WOL074-009 (9), WOL074-019 (19), and WOL074-029 (29)] with optimized physicochemical properties. To characterize the anti-inflammatory potential of substance 9, 19 and 29 *in vivo* we used the mouse model of imiquimod-induced psoriasis-like skin inflammation and the peptides were injected i. v. into mice with established disease. Injection of all 3 peptides significantly ameliorated ongoing skin inflammation as shown by the reduced epidermal thickness, markedly decreased levels of Th1 and Th17 cells, and the down-regulated levels of pro-inflammatory cytokines. Notably, the anti-inflammatory properties of 9 and 19 were comparable to those of KdPT whereas 29 showed an improved anti-inflammatory potential. Next, we investigated whether local application of 9, 19 or 29 might be sufficient to

ameliorate ongoing imiquimod-induced psoriasis-like skin inflammation. Therefore, psoriatic mice were topically treated with a vehicle cream or a cream containing 1% emulsified substance 9, 19 or 29. Mice locally treated with the 3 peptides showed a reduced epidermal thickness and a markedly decreased activation of effector cells in lesional skin. Interestingly, topical treatment was as effective as i.v. application of the compounds. Thus, these data show that 9, 19 and 29 are able to efficiently ameliorate ongoing inflammation in the skin. Because of the improved physicochemical properties 9, 19 and 29 may be formulated for topical application.

PP010 EFFECTS OF CHRONIC PSYCHOSOCIAL STRESS ON BONE METABOLISM IN ADOLESCENT MALE MICE

S. Foertsch[1], M. Haffner-Luntzer[2], J. Kroner[2], F. Gross[2], S. O. Reber[1], A. Ignatius[2]

[1]Laboratory for Molecular Psychosomatics, Clinic for Psychosomatic Medicine and Psychotherapy, University Ulm, Ulm, Germany, [2]Institute of Orthopedic Research and Biomechanics, University Medical Center Ulm, Ulm, Germany

In humans, depression is often paralleled by a high incidence of osteoporosis. In accordance, depressive-like behavior following chronic mild stress in mice was associated with decreased bone mass, probably due to increased corticosterone (CORT) levels. Given that chronic psychosocial stress induced by chronic subordinate colony housing (CSC) does not increase plasma CORT levels, we hypothesize that bone metabolism is differentially affected by chronic psychosocial stress. For this purpose, µCT analysis, histomorphometry and immunohistochemistry of the femurs as well as stress-related physiological parameters were assessed in CSC and respective single-housed control (SHC) mice on day 20 after CSC exposure. Cortical and trabecular thickness as well as bone mineral density were significantly increased after CSC, associated with higher osteocalcin expression in osteoblasts. Femur and tibia length were significantly reduced, whereas growth plate thickness was significantly increased. Runx2 expression was decreased in the hypertrophic and calcification zone of the growth plates, which may indicate reduced cartilage-to bone transition during endochondral ossification. Tyrosine hydroxylase (TH) protein expression was strongly upregulated in both the adrenal and growth plates of CSC mice, suggesting an involvement of the sympathetic nervous system (SNS). Furthermore, preliminary data suggest an enhancement of the innate but a reduced activity of the adaptive immune system in CSC mice. Together, these data indicate that chronic psychosocial stress increased appositional bone growth, whereas longitudinal bone growth was significantly diminished and that both, the SNS and the immune system might play a key role in this disturbed endochondral ossification.

PP11 LATE-ONSET COGNITIVE IMPAIRMENTS AFTER EARLY-LIFE STRESS ARE SHAPED BY INHERITED DIFFERENCES IN STRESS REACTIVITY

S. McIlwrick[1], T. Pohl[1], A. Chen[1,2], C. Touma[1,3]

[1]Department of Stress Neurobiology and Neurogenetics, Max Planck Institute of Psychiatry, Munich, Germany, [2]Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel, [3]Department of Behavioural Biology, University of Osnabrück, Osnabrück, Germany

Early-life stress (ELS) has been associated with lasting cognitive impairments and with an increased risk for affective disorders. A dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis is critically involved in mediating these long-term consequences of ELS. It remains unclear to what extent an inherited predisposition for HPA axis responsiveness influences the relationship between ELS and cognitive impairments, and which molecular mechanisms may be involved. To investigate this, we exposed animals of the stress reactivity mouse model, consisting of three independent lines selectively bred for high (HR), intermediate (IR) or low (LR) HPA axis reactivity, to ELS and assessed their cognitive performance, neuroendocrine function and hippocampal gene expression in early and in late adulthood. Our results show that HR animals that were exposed to ELS exhibited an HPA axis hyper-reactivity in early and late adulthood, associated with cognitive impairments in hippocampus-dependent tasks, as well as changes in transcripts involved in the regulation of HPA axis activity (*Crh*) and in neurotrophic action (*Bdnf*). In contrast, LR animals showed intact cognitive function across adulthood, with no change in stress reactivity. Intriguingly, LR animals that were exposed to ELS even showed signs of enhanced cognitive performance in late adulthood, which may be related to late-onset changes in the expression of *Crh* and *Crhr1* in the dorsal hippocampus. Collectively, our findings demonstrate that the lasting consequences of ELS at the level of cognition differ as a function of inherited predispositions and suggest that an innate tendency for low stress reactivity may be protective against these effects.

PP12 ALTERED B CELL HOMEOSTASIS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND NORMALIZATION OF REGULATORY B CELL FREQUENCIES IN TREATMENT RESPONDERS

D. Ahmetspahic[1,2], K. Schwarte[1,2], O. Ambrée[1,3], C. Bürger[1], V. Falcone[1], K. Seiler[1], M. Rahbar Kooybaran[1,2], L. Grosse[1], F. Roos[1], J. Scheffer[1], S. Jörgens[1], K. Koelkebeck[1], U. Dannlowksi[1,5], V. Arolt[1], S. Scheu[4*], J. Alferink[1,2*]

[1]Department of Psychiatry, University of Münster, Germany; [2]Cluster of Excellence EXC 1003, Cells in Motion, University of Münster, Germany; [3]Department of Behavioural Biology, University of Osnabrück, Germany; [4]Institute of Medical Microbiology and Hospital Hygiene, University of Düsseldorf, Germany; [5]Department of Psychiatry, University of Marburg, Germany

Pro-inflammatory activity and cell-mediated immune responses have been widely observed in patients with major depressive disorder (MDD). Besides their well-known function as antibody-producers, B cells play a key role in inflammatory responses by secreting pro- and anti-inflammatory factors. However, homeostasis of specific B cell subsets has not been comprehensively studied in MDD. In this pilot study, we characterized circulating B cell subsets of distinct developmental steps including transitional, naïve-mature, antigen-experienced switched, and non-switched memory cells, plasmablasts and regulatory B cells by multi-

parameter flow cytometry. In a 6-week follow-up, we further monitored the peripheral B cell pool in a small group of therapy responders with ≥ 30% HAM-D17 score reduction. We could demonstrate that frequencies of naïve $IgD^{+}CD27^{-}$ B cells, but not $IgD^{+}CD27^{+}$ memory B cells, were reduced in patients with MDD as compared to healthy donors (HD). Specifically, reduced percentages and numbers of $CD24^{+}CD38^{hi}$ transitional B cells, constituting recent bone marrow emigrants, were observed in MDD. Importantly, B cells with a regulatory phenotype expressing CD5 or co-expressing CD1d and CD5 were significantly reduced in MDD when compared to HD pointing towards a B cell dependent immunoregulatory process in MDD. A recovery specifically of transitional and regulatory B cells to levels observed in HD occurred in clinical responders after 6 weeks of therapy. This study demonstrates that patients with MDD harbor a compromised peripheral B cell compartment with a reduction of B cells with a regulatory phenotype. Clinical responders showed recovery of regulatory B cells pointing towards a functional involvement of this B cell subset in the pathogenesis of MDD.

PP13 GROWTH HORMONE-INDUCED SIGNALING: A NOVEL, INTRAFOLLICULAR NEUROENDOCRINE CONTROL OF HUMAN HAIR GROWTH

M. Alam[1, 2], D. A. Below[1], M. Bertolini[1,2], J. Chéret[2], R. Paus[1,3]

[1]Dermatology, Univ of Münster, Münster, Germany [2]Monasterium Laboratory, Münster, Germany [3]Dermatology Res Ctr, Univ of Manchester, Manchester, UK

Growth hormone (GH) and activation of its receptor (GHR) promote cell growth, proliferation, and differentiation either directly or via IGF-1 induction. While clinical case reports suggest that human hair follicles (HFs) may be GH-responsive, it is unknown whether GH exerts any functions in human HF biology. To explore this, we charted the expression of GH, GHR and growth hormone releasing hormone (GHRH), the hypothalamic neurohormone that stimulates pituitary GH expression and release, in human scalp HFs. So far, we have detected GH, GHR and GHRH protein expression in the ORS of human anagen VI HFs. qRT-PCR analysis revealed that human scalp HFs also transcribe GH, GHR and GHRH mRNA, supporting that human HFs are an extrapituitary source of GH production. qRT-PCR analysis showed GHR transcription decreases during HF regression (catagen HFs), whilst the level of the GH-inhibiting hormone, somatostatin (SST), was increased. Recombinant hGH (rGH, 100-200 ng/ml) induced premature catagen development *ex vivo* in female microdissected HFs, along with a significant increase of intrafollicular IGF-1 and TGFβ2 protein immunoreactivity. qRT-PCR analysis showed that hGH (300 ng/ml) treated HFs, reduced transcript levels of GHRH, GHR and SST, while GH and IGF-1 mRNA levels were relatively unchanged. This suggests that the catagen-promoting effects of GH onhuman HFs are rather IGF-1 independent. Interestingly, scalp HFs stimulation with GHRH (300ng/ml) *ex vivo* up-regulated GH transcription, supporting that GH is indeed transcribed intrafollicularly (e.g. via GHRH). Our study already shows that GHR-mediated signaling by intrafollicularly generated GH is a major novel neuroendocrine regulator of human hair growth.

PP14 MATHEMATICAL MODELLING OF THE NEUROENDOCRINE-IMMUNE SYSTEM IN RHEUMATOID ARTHRITIS

N. Amin[1], S. Binder[1], G. Pongratz[2], J. Triesch[3], M. Meyer-Hermann[1]

[1]Department of Systems Immunology, Braunschweig integrated Centre for Systems Biology and Helmholtz Centre for Infection Research, [2]University Hospital Regensburg, [3]Frankfurt Institute for Advanced Studies

During the last decades, the complex intercommunication between the neuroendocrine and the immune system and its regulatory role in systemic auto-inflammatory diseases have been extensively studied. Dysfunctions in any of these systems and their interconnections can result in imbalances in homeostatic mechanisms and might be one of the risk factors in the pathogenesis of rheumatoid arthritis (RA). In our study, we employ the descriptive and predictive power of mathematical modeling to investigate this hypothesis. Using ordinary differential equations, we describe the kinetics and nonlinear interactions between TNF-α, Noradrenaline and Cortisol, which play a key role in development of RA. This study is focused on three main topics: (I) The pathophysiology of the system to understand its behavior in healthy and RA conditions (ii) Determination of essential factors inducing the transition from the healthy to the RA phase (iii) Optimization of the current drug treatments in silico. Our model fits to the clinical data and succeeds in capturing the existing circadian dynamics of the NEI system in both healthy and RA individuals. The model reproduces the clinical data in the RA condition with respect to HPA axis dysfunction and sympathetic denervation of inflamed joints. The model is further used to optimize the scheduling and dosing of the glucocorticoid therapy. This study provides an interdisciplinary framework for studying the complexity of the NEI system, for a deeper understanding of how it is functioning and for determination of causative agents of NEI dysfunction.

PP15 THE SECONDARY TLR4 RESPONSE AND GLUCOCORTICOIDS ACT SYNERGISTICALLY ON MONOCYTES PROMOTING AN ANTI-INFLAMMATORY AND PRO-RESOLVING PHENOTYPE

K. Barczyk-Kahlert[1], Y. Kusche[1], J. Ehrchen[2], J.Roth[1]

[1]Institute of Immunology, University of Münster; [2]Department of Dermatology, University Hospital Münster

Monocytes and macrophages are central components of the immune system. Glucocorticoids (GC) are still the most potent immunosuppressive agents used in the treatment of chronic inflammatory and autoimmune diseases. We have shown that treatment of naïve monocytes with GC does not cause a global suppression of monocytic effector functions, but rather induces specific differentiation of these cells to an anti-inflammatory phenotype. However, the impact of GC on proinflammatory monocytes is still not well defined. The aim of these studies was to analyse the effects of GC on lipopolysaccharide (LPS)-triggered proinflammatory monocytes. Human monocytes were stimulated with GC and/or LPS. Microarray analysis was performed using Affymetrix Human Genome U133 2.0 Plus Arrays. Bioinformatic analysis was carried out to

determine differentially expressed genes, biological functions and key transcription factors (TFs) activated in LPS-GC-stimulated monocytes. Functional tests were performed to confirm specific functions of LPS-GC-stimulated monocytes identified in silico. The expression and nuclear localization of TFs was confirmed in western blot. As expected, GC led to suppression of many LPS-induced proinflammatory genes. Surprisingly, GC and LPS act synergistically on the expression of many genes involved in macrophage polarization, immune modulation and resolution of inflammation. GC-treatment of LPS-activated monocytes induced diminished adhesion but enhanced migration, chemotaxis, phagocytosis and production of pro-resolving lipid mediators. We identified Foxo3a, CEBPB and Notch3 as key TFs orchestrating the GC-LPS induced differentiation of this anti-inflammatory phenotype in monocytes. GC do not simply suppress LPS-mediated activation of monocytes but rather reprogram their differentiation pathway toward an anti-inflammatory and pro-resolving phenotype.

PP16 IL-1β IN THE BRAIN ACTIVATES A CENTRAL-TO-PERIPHERY PATHWAY OF CYTOKINE INDUCTION

H. Besedovsky[1], A. Randolf[1], E. Roggero[2], A. del Rey[1]

[1]Inst. of Physiology and Pathophysiology, University of Marburg, Germany; [2]Dept. of Physiology, Faculty of Medicine, Universidad Abierta Interamericana and Inst. of Immunology, National University of Rosario, Argentina

Besides its immunological functions, IL-1β also modulates the activity of the hypothalamus-pituitary-adrenal axis, affects glucoregulation, and supports mechanisms based on synaptic plasticity such as LTP, learning, and memory. There is evidence that IL-1β can induce its own production in immune organs and in the brain when administered peripherally. Here we explored the possibility that: 1) IL-1b activates the expression of its own gene and those of other cytokines when injected directly into the brain; 2) acting initially at central levels, IL-1b can also promote its expression and that of other cytokines in the spleen, a main immune organ. Intracerebroventricular (i.c.v.) administration of IL-1β into mice resulted in marked hypoglycemia and increased corticosterone blood levels, and in increased IL-1β, IL-1ra, IL-6, and TNFα gene expression in the hypothalamus and hippocampus. IL-4 and IL-10 were hardly detectable in these brain areas. IL-1, IL-1ra, IL-6, and IL-10 gene expression was also increased in the spleen of the same mice, while TNFα gene expression was not altered and IL-4 expression was decreased. Thus, administration of IL-1β in the brain results in the activation not only of central but also of peripheral cytokine networks, suggesting a brain-to-periphery pathway of cytokine modulation. Besides physiologic functions in the brain, this pathway may be particularly relevant in neuropathologies during which brain-borne cytokines may also affect peripheral immune responses. Supported by the DFG (RE 1451/3-1).

PP17 DEEPENING SLEEP BY AUDITORY STIMULATION IMPACTS THE ENDOCRINE AND LYMPHOCYTE PROFILE IN HEALTHY MEN

L. Besedovsky[1], H.-Viet V. Ngo[1], S. Dimitrov[1], R. Lehmann[2], A. Fritsche[3], J. Born[1]

[1]Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen; [2]Central Laboratory, Department for Diagnostic Laboratory Medicine, University of Tübingen; [3]Department of Internal Medicine IV, University of Tübingen

Sleep is essential for maintaining health. Slow-wave sleep (SWS), the deepest sleep stage, which is hallmarked by slow oscillations (SOs) in the electroencephalogram, appears of particular relevance in this context. SWS is associated with a unique endocrine constellation comprising minimum cortisol and high prolactin, growth hormone and aldosterone levels, and thereby presumably fosters efficient adaptive immune responses. Yet, whether SWS causes these changes is unclear. Here, we enhanced SWS in men by closed-loop stimulation of SOs, i.e., by delivering tones in synchrony with endogenous SOs occurring during sleep. Concomitantly to deepening SWS, auditory stimulation reduced nadir cortisol concentrations and enhanced prolactin and aldosterone levels. T and B lymphocyte counts were also decreased, likely reflecting the redistribution of these cells to lymphoid tissues. Thus, auditory closed-loop stimulation of SOs is not only an easy-to-use tool for probing SWS functions but also a promising treatment approach for conditions, like depression and aging, where disturbed sleep coalesces with specific hormonal and immunological dysregulations.

PP18 IMMUNOSUPPRESSION IN INFLAMMATION- THE ROLE OF PRO- AND ANTI-INFLAMMATORY T-CELL SUBSETS IN A HUMAN, EXPERIMENTALLY INDUCED ENDOTOXINAEMIA MODEL

A. Brinkhoff[1,2,] A. Siebericbs[1,2], H. Engler[1], S. Benson[1], S. Dolff[2,3], J. Korth[2], B. Wilde[2], A. Kribben[2], O. Witzke[2,3], M. Schedlowski[1]

[1]Institute for Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University Duisburg-Essen, Essen, Germany; [2]Department of Nephrology, University Hospital Essen, University Duisburg-Essen, Essen, Germany, [3]Department of Infectious Diseases, University Hospital Essen, University Duisburg-Essen, Essen, Germany

Objective: Systemic inflammatory response syndrome (SIRS) is a multifactorial inflammatory response of an organism to infection or endotoxins, e.g. lipopolysaccharides (LPS). Two distinct overlapping phases of the immune response, a pro- and anti-inflammatory phase, can be observed in SIRS. T-cells provide pro- and anti-inflammatory functions. Regulatory T-cells (Tregs) have a pivotal role in immune regulation via limiting inflammatory conditions by producing interleukin (IL)-10, which is the most important anti-inflammatory cytokine. **Method:** In a crossover designed placebo-controlled study, 20 healthy male volunteers received an intravenous injection of either LPS (0.8ng/kg body weight) or a placebo (saline 0.9%). Quantification of $CD3^+/CD4^+/CD8^+$T-cells and intracellular cytokines was done by flow cytometry at baseline and 3 hours after LPS/placebo injection. Complete blood cell counts were obtained

with an automated hematology analyzer and cytokines were quantified by ELISA. **Results:** Circulating leukocytes were increased 3 hours after LPS injection with a maximum rise of neutrophils after 6 hours. CD3+/CD4+/CD8+T-cells showed a significant decrease. Intracellular proinflammatory T-cell cytokine production such as Interferon-γ (IFN-γ), interleukin (IL)-2 and interleukin (IL)-17A from T helper cells (TH, $CD3^+/CD8^-$) significantly decreased (IFN-γ of TH: 17.03% vs. 5,02%; IL-2 and IL-17A production of TH: 41.55% vs. 37.17%; 1.15% vs. 0.63%). The IL-10 production of TH was stable (0.83% vs. 0.71%). The systemic IL-10 level significantly increased (0.57 pg/ml vs.16.66 pg/ml). **Conclusion:** The IL-10 release increased in the early phase of SIRS. The Treg compartment was stable. Taken together, this may contribute to the inhibition of pro-inflammatory responses via suppression of proinflammatory T-cell subsets.

PP19 TH17 AS A PREDICTOR OF RESPONSIVENESS TO ADD-ON CYCLOOXYGENASE-2 (COX-2) THERAPY IN MAJOR DEPRESSIVE DISORDER

J. Schnell[1], G. Arteaga-Henríquez[1,2], B. Leitner[1], E. Weidinger[1], V. Arolt[3], H. A Drexhage[2], N. Müller[1]

[1]Dept. of Psychiatry, Ludwig-Maximilians-University, Munich, Germany; [2]Dept. of Immunology, Erasmus MC, Rotterdam, The Netherlands; [3]Dept. of Psychiatry, University Hospital Muenster, Muenster, Germany

A proinflammatory state in a subgroup of depressed patients has been reported repeatedly, for example an increase in interleukin-6 (IL-6) is well documented. IL-6 drives the production of T helper 17 (Th17) cells, which play a significant role in autoimmune disease and its inflammatory response. Treatment with COX-2 inhibitors down-regulate increased inflammatory markers. COX-2 is constitutively expressed in the most important areas of the brain responsible for cognition. Therefore a treatment of depression with COX-2 in combination with an antidepressant might lead to a better clinical outcome. *Aim:* To predict responsiveness to add-on COX-2 inhibition treatment using immune cellular assays. *Design:* Double-blind controlled investigation treating 43 MDD patients with a 6 week treatment of sertraline plus placebo or sertraline plus celecoxib. Immune outcomes were compared to those of healthy controls (HC). Before therapy the subset profile of circulating Th17 cells (via FACS) was studied and related to therapy outcome. *Results:* Patients did respond (HAMD-17 $\geq$ 60%) significantly better to the add-on therapy. The group who did not respond to the add-on therapy was characterized by a high level of Th17 cells. The percentage of Th17 cells within the MDD group was significantly reduced compared to the HC. *Conclusion:* Our study indicates that a COX-2 add-on treatment is superior to a treatment with an SSRI alone and that a pre-therapy immune paradigm of a Th17 cell deficit heralds responsiveness to the add-on therapy.