15th GEBIN Conference 2023

28-30th September 2023 Ulm / Germany

Educational Short Course

27-28th of September

Dear Colleagues,

Welcome to the beautiful city of Ulm for the GEBIN conference 2023!

On behalf of the Steering Committee of the German Endocrine-Brain-Immune-Network (GEBIN) it is our great pleasure to welcome you to the 15th conference of the GEBIN that will be held in Ulm, September 28-30th, 2023.

Since more than 30 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 2023 conference will be divided into several thematic sessions including Rhythms and "Blues", Stress, Immunoregulation, Inflammation, Neuro-Endocrine and Neuro-Immune-Endocrine. In addition, the conference will comprise of three keynote lectures, held by the internationally recognized experts Prof. Dr. Michael Eriksen Benros (University of Copenhagen, Denmark), Prof. Dr. Christopher A. Lowry (University of Colorado, Boulder, USA) and Prof. Dr. Martin Heni (Ulm University Medical Center, Germany). A Poster session will also further provide a forum for interactions between GEBIN newcomers and established scientists.

Moreover, we are proud to again offer an Educational Short Course for students. The course will be hosted by Prof. Dr. Adriana del Rey (Philipps University of Marburg, Germany) and will take place on September 27-28th, 2023 prior to the official start of the GEBIN Conference.

With kind regards

Stefan Reber, Local Organizer

Silvia Capellino and Harald Engler, on behalf of the GEBIN Steering Committee

Scientific Committee*

Prof. Dr. Judith Alferink, Münster
Prof. Dr. Hugo Besedovsky, Marburg
Prof. Dr. Markus Böhm, Münster
Prof. Dr. Jan Born, Tübingen
Prof. Dr. Silvia Capellino, Dortmund (Spokeswoman)
Prof. Dr. Harald Engler, Essen (Spokesman)
Prof. Dr. Bernd Fiebich, Freiburg
Prof. Dr. Ulrike Gimsa, Dummerstorf
Prof. Dr. Stefan Gold, Berlin
Prof. Dr. Tanja Lange, Lübeck
Prof. Dr. Norbert Müller, München
Prof. Dr. Eva Peters, Berlin/Giessen
Prof. Dr. Georg Pongratz, Düsseldorf
Prof. Dr. Stefan Reber, Ulm
Prof. Dr. Adriana del Rey, Marburg
Prof. Dr. Nicolas Rohleder, Erlangen-Nürnberg
Prof. Dr. Christoph Rummel, Giessen
Prof. Dr. Manfred Schedlowski, Essen
Prof. Dr. Markus Schwarz, München
Prof. Dr. Volker Stefanski, Stuttgart
Prof. Dr. Rainer Straub, Regensburg
Prof. Dr. Eberhard Weihe, Marburg

Local Organizing Committee

Prof. Dr. Stefan Reber & Team, Ulm
Prof. Dr. Silvia Capellino, Dortmund (GEBIN Spokeswoman)
Prof. Dr. Harald Engler, Essen (GEBIN Spokesman)

*According to the Gebin homepage (www.gebin.org) as accessed on July 17th 2023.

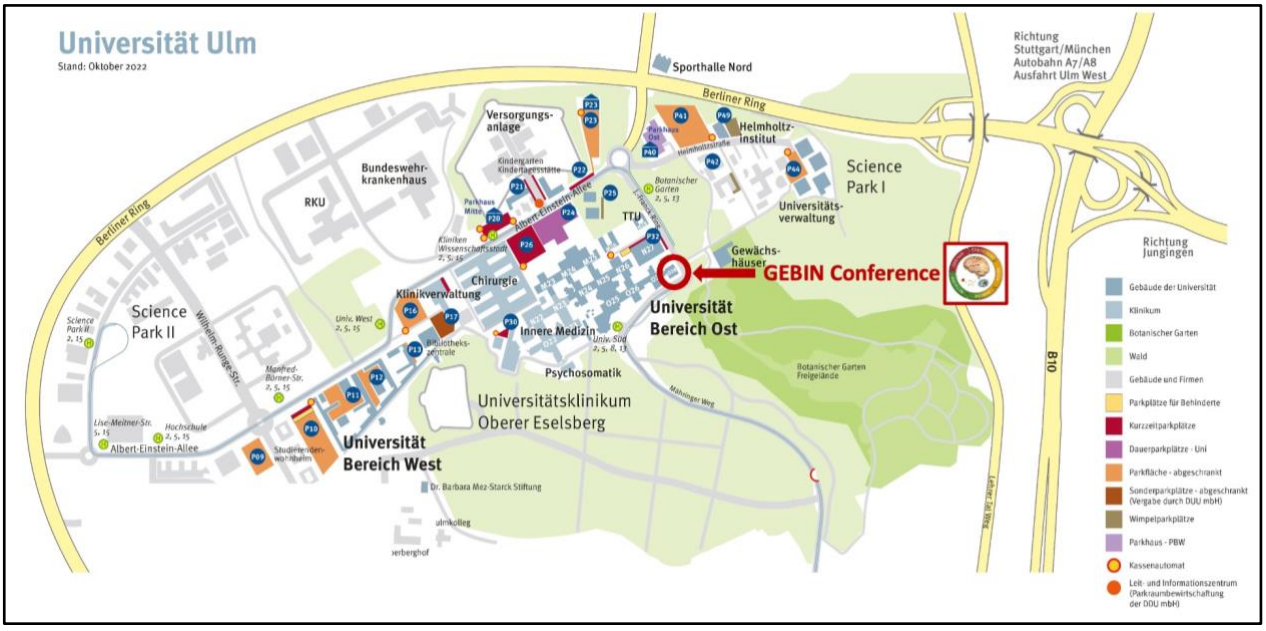
Online Information about the GEBIN 2023 Conference

Information about the GEBIN 2023 Conference can be found on the GEBIN 2023 Conference homepage, accessable via the following link or QR code below.

Congress Venue

The GEBIN 2023 Conference will take place in H22/ Building O28 at Ulm University. A detailed map of Ulm University, a description of how to get to the 2023 GEBIN Conference Venue at Ulm University and a map of Ulm public transportation (Tram/Bus lines) can be found below.

Travel by car: From the *Autobahn A-8 Stuttgart – München* take the exit *Ulm-West* with direction to Ulm, from there take the second exit ***Universität / Wissenschaftsstadt*** (Science City). Follow the left lane; at the traffic light turn left onto the campus.

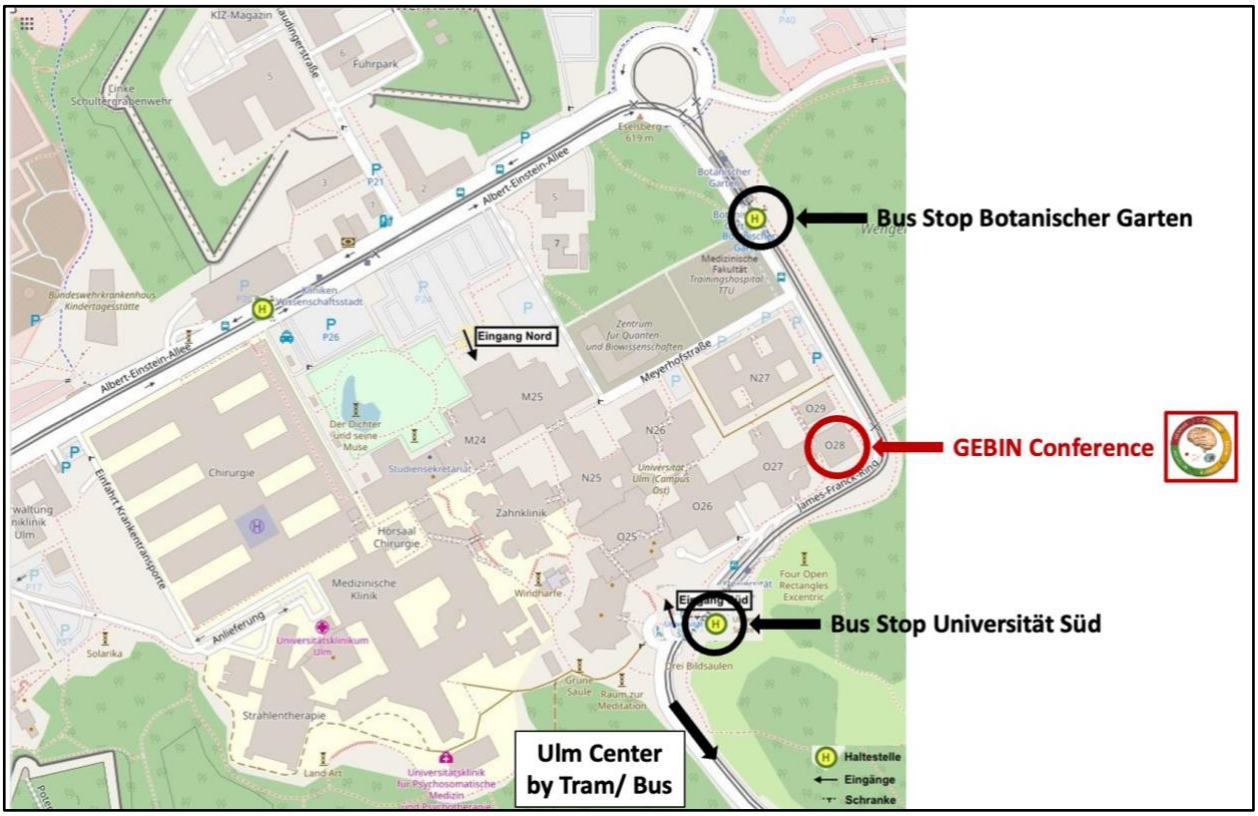


Map indicating accessability of Ulm University by car (can also be found via the follwing link).

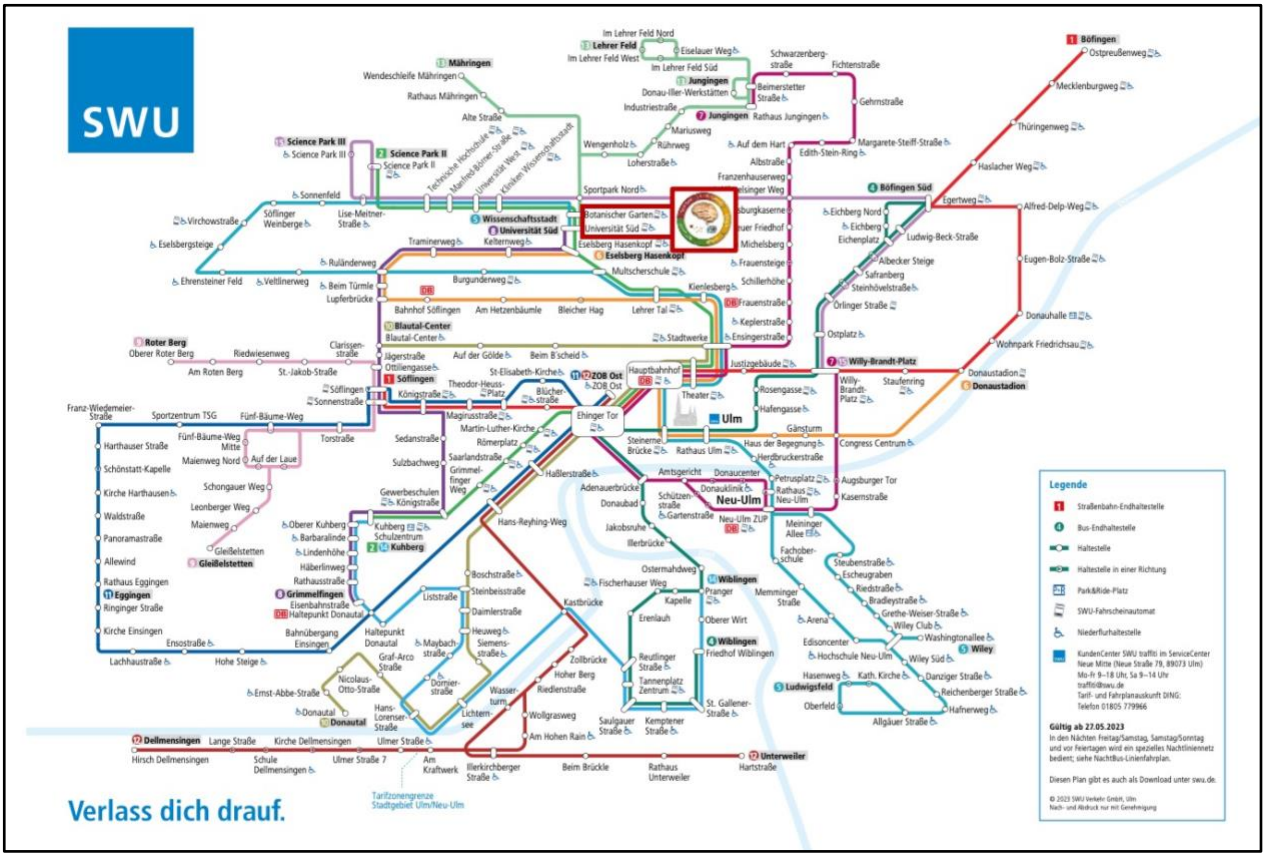
Travel by train: Following arrival at Ulm Main Station, the 2023 GEBIN Conference venue at Ulm University is easily accessible either by Tram (Line 2, destination "Science Park") or Bus (Number 5, destination "Science Park"), departing directly in front of Ulm Main Station. On weekdays the

tram runs every 10 minutes and takes about 10 minutes to arrive at Ulm University. At Ulm University, we recommend taking one of the following Bus/Tram stops: ***Universität Süd*** or ***Botanischer Garten***. Getting back to the city center is possible by Tram (Line 2, destination "Kuhberg") or Bus (Number 5, destination "Ludwigsfeld/Wiley").

To get to the 2023 GEBIN Conference Venue please follow the respective signs.



Map indicating accessibility of Ulm University by Bus/Tram (can also be found via the follwing link).



Map indicating public transportation system of Ulm (also accessible via the following link).

Official Language

The official language of the conference is English.

Registration

Most people have already preregistered via the homepage of the Conference. 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 200 € for senior scientists and 140 € for Bachelor-/Master-/ PhD Students.

Educational Short Course

The GEBIN offers an Educational Short Course organized by Prof. Dr. Adriana del Rey, Philipps University of Marburg, Germany.

Time: September 27th 2023, 13:30 – 19:00 and September 28th 2023, 09:00 – 13:00.

Venue: O28, Room 2001.

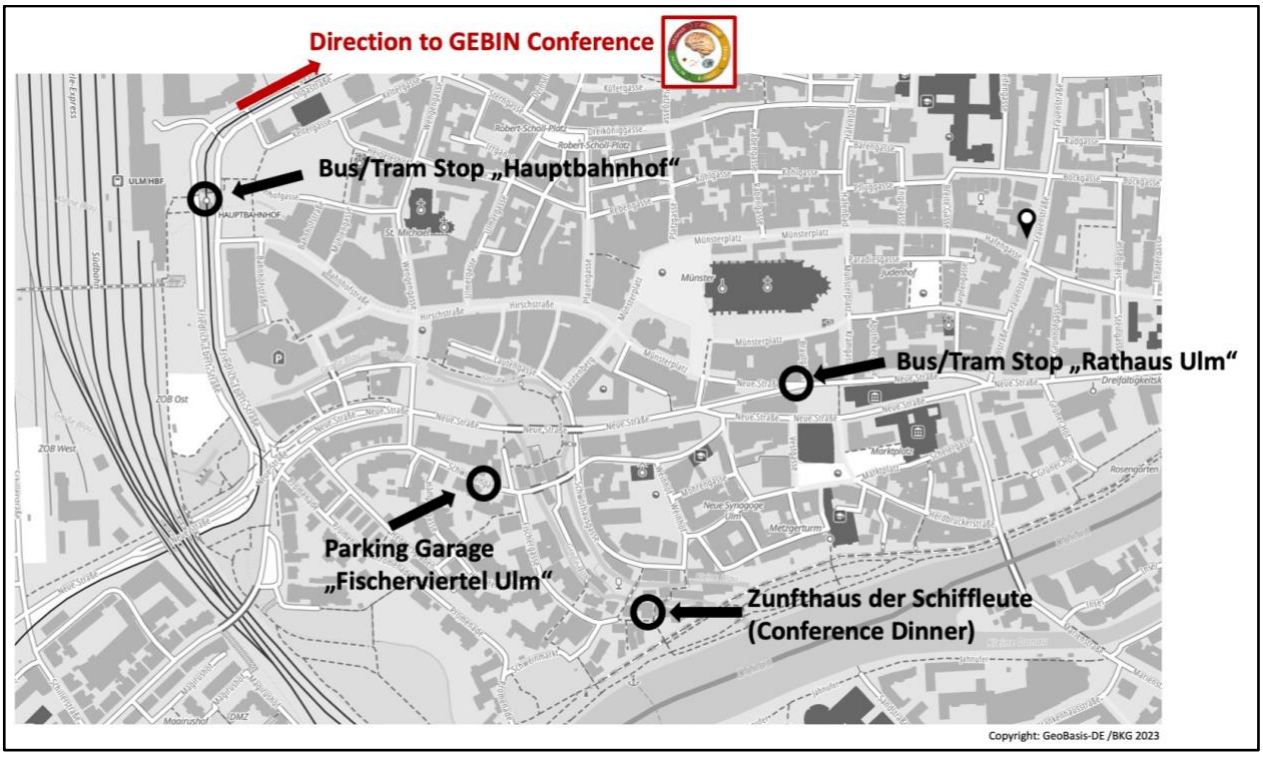
For further details of the course and for registration, please visit the GEBIN 2023 Conference homepage (accessable via the following link or QR code above) or contact Prof. Dr. Adriana del Rey (Philipps University of Marburg, Germany): e-mail: delrey@mailer.uni-marburg.de.

Presentations

Contributions are presented in form of short presentations and posters. The time for each presentation is 10 min plus 5 min of discussion. Please adhere strictly to this time limit. Presentations should be uploaded (Powerpoint (.pptx) file) onto the presentation computer in the morning prior to the start of the first session of the day. Posters should be mounted at the poster walls before the start of the conference and should stay available until the end of the conference. The size of the poster board is 100 cm width x 150 cm height. Mounting materials will be provided. Please remove your poster after the end of the conference.

Conference Dinner

The Conference Dinner will take place on Friday evening, September 29th 2023 at 18:00, at the "Zunfthaus der Schiffleute" (Fischergasse 31, 89073 Ulm), located in the "Fischerviertel" of Ulm. If you arrive by Bus/Tram, we recommend taking the Bus stop "Rathaus Ulm". If you arrive by Car, the nearest parking garage is "Fischerviertel Ulm". A map of Ulm indicating the Bus/Tram Stops, Parking Garage and the location of the Conference Dinner can be found below.



Map indicating the city center of Ulm.

Catering

Free-of-charge catering for all registered participants of the GEBIN Conference 2023 will be provided during coffee and lunch breaks, the welcome reception and the conference dinner (Including one starter, one main course and one desert as well as one drink per participant).

Awards

GEBIN Award 2023

The GEBIN and the Foundation "Immunität und Seele" call for applications for the GEBIN "Immunität und Seele" Award for excellent research on the immune system, inflammatory mechanisms, and related therapeutic approaches in the field of behavioral sciences or psychiatric disorders.

The prize money is 2000 €!

The award is provided to young researchers – preferably before or within the first 5 years after their doctorate – for innovative basic or clinical research. Applicants should work at a German scientific institution. Applications should be submitted until July 31st, 2023 (deadline) and must include:

- Curriculum vitae
- Summary of the major research activities (not exceeding one page)
- List of relevant publications (accepted or published) not older than two years

The award ceremony will take place at the GEBIN Meeting in Ulm (September 28th -30th, 2023; for details see the program below or follow the link). Submissions and Posters will be selected by a jury composed of members of the GEBIN Steering Committee and the Foundation "Immunität und Seele". All decisions are final. The jury is exempt from legal liability. Please send applications by email to info@gebin.org

Young Presenter Awards 2023

The GEBIN and the Foundation "Immunität und Seele" will provide 3 Young Presenter Awards. The prize money for each Award is 200 €!

The award ceremony will take place at the GEBIN Meeting in Ulm (September 28th -30th, 2023; for details see the program below or follow the link). Poster Awards will be selected by a jury composed of members of the GEBIN Steering Committee and the Foundation "Immunität und Seele". All decisions are final. The jury is exempt from legal liability.

The GEBIN Conference 2023 is supported by

Stiftung Immunität und Seele

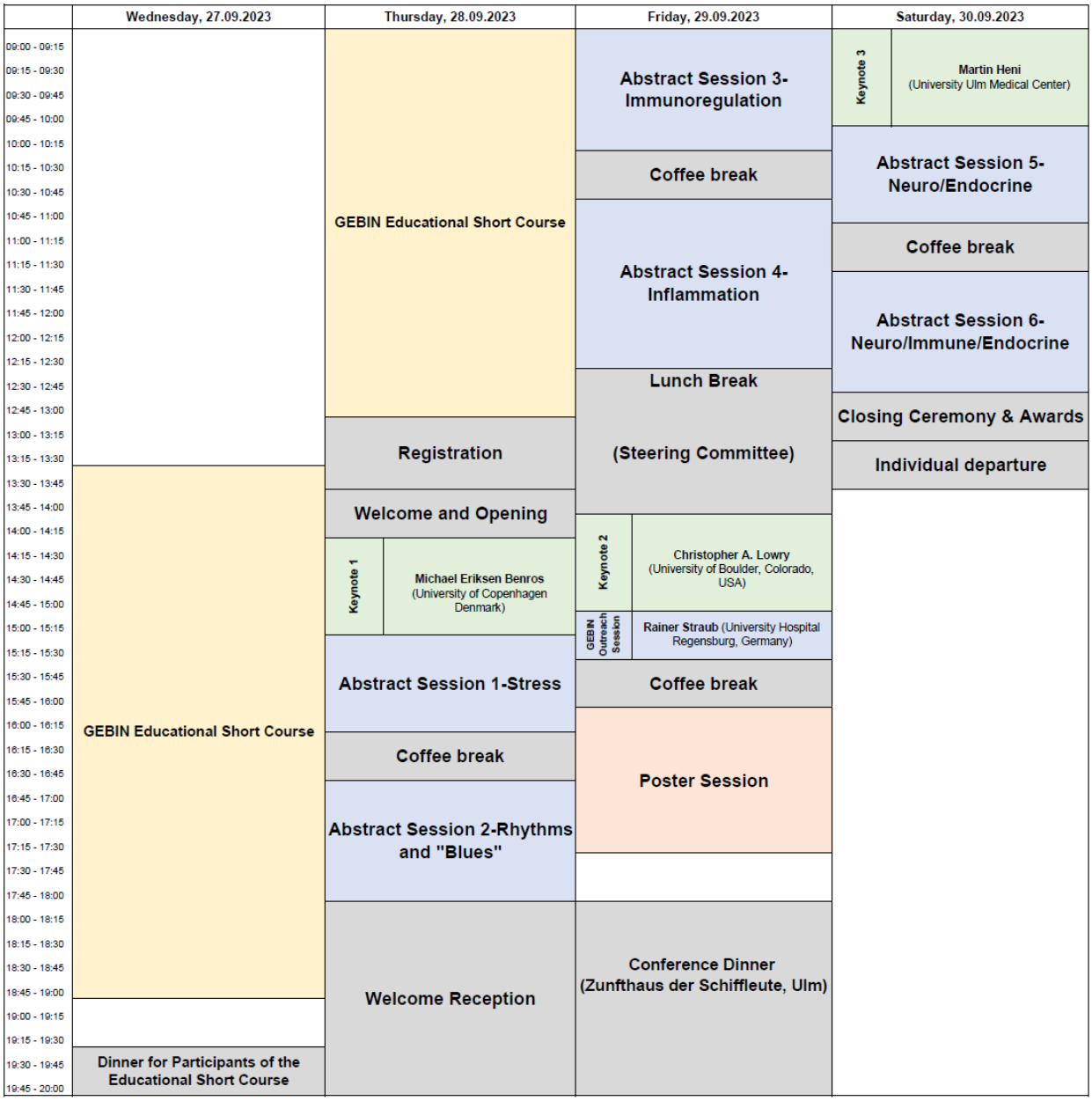
Collaborative Research Centre 1149

"Danger Response, Disturbance Factors and Regenerative Potential after Acute Trauma

Further Information

Further information about the GEBIN can be found at: www.gebin.org.

Program



Scheme indicating the timeline of the 12th GEBIN Educational Short Course and all main sessions of the 15th GEBIN Conference. A more detailed version of this program can be found below and via the following link.

Program of the 15th GEBIN Conference

Venue: All presentations will be held at H22/ Building O28 at Ulm University. A detailed map of Ulm University can be found above or accessed via the follwing link.

Day 1: Thursday, September 28th, 2023

13:00 – 13:45	**Registration**
13:45 – 14:15	**Welcome and Opening**
14:15 – 15:15	Keynote 1
Chair:	*Norbert Müller (Ludwig-Maximilian-University Munich, Germany)*
	Michael Eriksen Benros (University of Copenhagen, Denmark) Immunopsychiatry – Evidence from Large Scale Studies to Detailed Clinical CSF Studies.
15:15 –16:15	Abstract Session 1: **Stress**
Chairs:	*Judith Alferink (University Hospital Münster, Germany) & Harald Engler (University Hospital Essen, Germany)*
15:15 – 15:30	**OP1**: Porcine blood cell and brain tissue energy metabolism: effects of "Early Life Stress" *Nadja Carina Abele (Ulm University Medical Center, Ulm, Germany)*
15:30 – 15:45	**OP2**: Lactational stress influences milk composition but has little effect on stress responses of offspring in domestic pigs: Evidence for resilience? *Ulrike Gimsa (Research Institute for Farm Animal Biology (FBN), Germany)*
15:45 – 16:00	**OP3**: The influence of everyday emotions on mucosal immunity: A multi-level structural equation modeling approach *Lennart Seizer (University of Tübingen, Germany)*
16:00 – 16:15	**OP4**: Psychological or inflammatory stimulation in mice: investigating how neutropenia affects heart rate variability as a readout parameter. *Leona Bähr (Justus Liebig University Giessen, Germany)*

16:15 – 16:45	**Coffee Break**

16:45 – 18:00 Abstract Session 2: **Rhythms and "Blues"**

Chairs: *Iris Kolassa (Ulm University, Germany) & Ilia Karatsoreos (University of Massachusetts Amherst, USA)*

16:45 – 17:00 **OP5**: Immune signature of multiple sclerosis-associated depression
Jelena Brasanac (Charite Universitätsmedizin Berlin, Germany)

17:00 – 17:15 **OP6**: Characterisation of Circulating Dendritic Cells in Major Depressive Disorder
Anna-Lena Boller (Universitätsklinikum Münster, Germany)

17:15 – 17:30 **OP7**: The circadian system, sleep, and platelets in healthy individuals and in patients with systemic sclerosis
Tanja Lange (University of Lübeck, Germany)

17:30 – 17:45 **OP8**: Circadian influences in a mouse model of autoimmune skin blistering disease
Sarah Stenger (University of Luebeck, Germany, Germany)

17:45 – 18:00 **OP9**: Alterations of DNA Repair in Immune Cells of Patients with Posttraumatic Stress Disorder and Their Relation to Genomic Integrity and Traumatic Stress
Matthias Mack (Ulm University, Germany)

18:00 – 20:00	**Welcome Reception**

Day 2: Friday, September 29th, 2023

09:00 – 10:15 Abstract Session 3: **Immunoregulation**

Chairs: *Laura Heiß-Lückemann (University Hospital Essen, Germany) & Dominik Langgartner (Ulm University Medical Center, Germany)*

09:00 – 09:15 **OP10**: Omega-3 polyunsaturated fatty acids modulate the lung-brain axis of communication during LPS-induced ARDS
Julia Schaeffer (Justus-Liebig-University, Germany)

09:15 – 09:30 **OP11**: Daily pet contact during urban upbringing ameliorates the inflammatory stress-response during adulthood

Dominik Langgartner (Ulm University Medical Center, Germany)

09:30 – 09:45 **OP12**: Deciphering neuroprotective effects of n-3 polyunsaturated fatty acids and related impacts of adipokines using organotypic hippocampal slice and primary neuroglial cell cultures.
Martin Feldotto (Justus Liebig University Giessen, Germany)

09:45 – 10:00 **OP13**: *Mycobacterium vaccae* ATCC 15483 immunization as an intervention for Western diet-induced physiological and behavioral changes in adolescent male mice
Luke Desmond (University of Colorado Boulder, USA)

10:00 – 10:15 **OP14**: Effects of *Mycobacterium vaccae* ATCC 15483 on biobehavioral health outcomes following a "two-hit" model of chronic disruption of rhythms and a Western diet in male and female C57BL/6N mice
Lamya'a M. Dawud (University of Colorado, USA)

10:15 – 10:45 Coffee Break

10:45 – 12:30 Abstract Session 4: **Inflammation**

Chairs: *Tanja Lange (University of Lübeck, Germany) & Christoph Rummel (Justus Liebig University Giessen, Germany)*

10:45 – 11:00 **OP15**: Interplay of inflammation and negative mood on visceral pain perception - A randomized controlled fMRI trial in healthy volunteers
Franziska Labrenz (Ruhr-University Bochum, Germany)

11:00 – 11:15 **OP16**: Autoantibodies Against Surface Molecules are Altered in Fibromyalgia Syndrome
Finn Luebber (Universität zu Lübeck, Germany)

11:15 – 11:30 **OP17**: Neutropenia exaggerates the inflammatory response in the brain and periphery during LPS-induced severe systemic inflammation
Jessica Hernandez (Justus-Liebig University, Germany)

11:30 – 11:45 **OP18**: Treatment expectation effects on inflammation-induced bodily sickness symptoms and mood disturbances in human experimental endotoxemia
Justine Schmidt (University Hospital Essen, Germany)

11:45 – 12:00 **OP19**: Fatigue assessed by FACIT-F subscale correlates with patients' perception of symptom severity in psoriatic arthritis
Hanna Grasshoff (University of Lübeck/University Medical Center Schleswig-Holstein, Germany)

12:00 – 12:15	**OP20**: Induction of negative treatment expectation in an animal model of endotoxin-induced sickness *Dombrowski, Kirsten (University Hospital Essen, Germany)*
12:15 – 12:30	**OP21**: Hypoxia priming aggravates LPS induced systemic inflammatory response in vivo in humans *Marie Jakobs (University Medicine Essen, Germany)*
12:30 – 14:00	**Lunch Break**
12:30 – 14:00	Meeting of the Steering Committee during lunch break
14:00 – 15:00	Keynote 2
Chair:	*Stefan O. Reber (Ulm University Medical Center, Germany)*
	Christopher A. Lowry (University of Colorado, Boulder, USA) Anti-inflammatory and immunoregulatory strategies for prevention and treatment of psychiatric disorders: focus on microglial priming and neuroinflammation.
15:00 – 15:30	GEBIN Outreach Session
Chair:	*Manfred Schedlowski (University Hospital Essen, Germany)*
	Neuroimmunomodulation: Journal Report *Rainer H. Straub (Editor-in-Chief)*
15:30 – 16:00	**Coffee Break**
16:00 – 17:30	Poster Session
18:00	**Conference Dinner** at the "Zunfthaus der Schiffleute" in Ulm (open end)

Day 3: Saturday, September 30th, 2023

09:00 – 10:00	Keynote 3
Chair:	*Rainer H. Straub (University Hospital Regensburg, Germany)*
	Martin Heni (Ulm University Medical Center, Germany) The insulin resistant brain: impact on whole-body metabolism and body fat distribution.
10:00 – 11:00	Abstract Session 5: **Neuro-Endocrine**
Chairs:	*Markus Böhm (University Hospital Münster, Germany) & Martin Hadamitzky (University Hospital Essen, Germany)*
10:00 – 10:15	**OP22**: The sympathetic nervous system - fat/muscle connection: an adaptive hypertensive program *Rainer H. Straub (University Hospital Regensburg, Germany)*
10:15 – 10:30	**OP23**: Melatonin synergizes with vemurafenib/cobimetinib-affected bioenergetic and proto-oncogenic pathways in human melanoma *Konrad Kleszczynski (University of Münster, Germany)*
10:30 – 10:45	**OP24**: The memory of the fatty acid system and its role for the immune system and the brain *Rainer H. Straub (University Hospital Regensburg, Germany)*
10:45 – 11:00	**OP25**: Neuroimmune responses to intranasal poly(I:C) are primed by time of day *Gregory Pearson (University of Massachusetts Amherst, USA)*
11:00 – 11:30	**Coffee Break**
11:30 – 12:45	Abstract Session 6: **Neuro-ImmuneEndocrine**
Chairs:	*Katharina Hillerer (Research Institute for Farm Animal Biology (FBN) Dummerstorf, Germany) & Silvia Capellino (Leibniz Research Centre for Working Environment and Human Factors Dortmund, Germany)*
11:30 – 11:45	**OP26**: Does the chronic beta2 adrenergic receptor stimulation of asthma patients alter systemic NK cell function?

Martin Obholzer (Leibniz Research Centre for Working Environment and Human Factors Dortmund, Germany)

11:45 – 12:00 **OP27**: MASP-3, and not MASP-1, is the main lectin pathway associated complement protease in mouse brain: evidence for a MASP-3/C3 complosome in astrocytes.
Martin K.H. Schäfer (University of Marburg, Germany)

12:00 – 12:15 **OP28**: Sex-specific effects of dopaminergic stimulation on peripheral immune cell response
Silvia Capellino (Leibniz Research Centre for Working Environment and Human Factors Dortmund, Germany)

12:15 – 12:30 **OP29**: TBI is associated with fast DC maturation and splenic immune modulation
Florian olde Heuvel (Ulm University Medical Center, Germany)

12:30 – 12:45 **OP30**: Sleep promotes T-cell migration towards CCL19 via growth hormone and prolactin signaling in humans
Estefania Martinez-Albert (Ludwig Maximilians University, Munich, Germany)

12:45 – 13:15 Closing Ceremony & Awards

13:15 – 13:45 Individual Departure

Abstracts of the 15th GEBIN Conference

Keynotes

Keynote 1

Immunopsychiatry – Evidence from Large Scale Studies to Detailed Clinical CSF Studies

Michael Eriksen Benros
University of Copenhagen, Denmark

Utilizing Danish nationwide registers we have consistently displayed that infections and autoimmune diseases increases the risk of developing severe mental disorders in a dose-response relationship, where the risk of severe mental disorders particularly increases with the number of infections exposed to and in a temporal manner. Utilizing large national biobank data, we have shown a small immunogenetic contribution with moderate correlation between the genetic susceptibility for infections and mental disorders. Moreover, at diagnosis there are elevated levels of inflammatory markers in the blood and studies on the cerebrospinal fluid surrounding the brain have shown some evidence for elevated immune markers in the CSF and signs of disrupted blood-brain barrier in some of the patients. Interestingly, our meta-analyses of randomized clinical trials have shown that anti-inflammatory treatment seems to be effective for depression and depressive symptoms and to some extent also for psychotic disorders. However, studies identifying subgroups that would be most likely to respond to immune modulating add-on treatment are still warranted to pave the field forward.

Keynote 2

Anti-inflammatory and immunoregulatory strategies for prevention and treatment of psychiatric disorders: focus on microglial priming and neuroinflammation

Christopher A. Lowry
Department of Integrative Physiology, University of Colorado, Boulder, USA

Evidence suggests that chronic low-grade inflammation is a risk factor for stress-related psychiatric disorders, including anxiety disorders, mood disorders, and trauma- and stressor-related disorders, such as posttraumatic stress disorder (PTSD). For example, biomarkers of inflammation in active military personnel, at baseline, prior to exposure to stress or trauma, predict risk of development of PTSD after deployment. In addition, persons with a diagnosis of PTSD have increased biomarkers of "leaky gut", including increased plasma concentrations of lipopolysaccharide, a component of the outer membrane of gram-negative bacteria, and lipopolysaccharide binding protein (LBP). At the same time, persons with a diagnosis of PTSD have decreased numbers and function of regulatory T cells (Treg) and a higher risk of developing future autoimmune disorders, suggesting an impaired capacity to regulate the inappropriate inflammation. Here we consider the hypothesis that increased inflammation in persons living in modern urban environments is due to a failure of immunoregulation, i.e., a failure of the balanced expression of regulatory and effector T cells, which is known to be dependent on microbial signals. In this talk, I will highlight preclinical studies showing that treatment with bacterial "Old Friends", i.e., bacteria with anti-inflammatory and immunoregulatory properties, can prevent stress-induced exaggeration of inflammation, neuroinflammation, and microglial priming, as well as promote stress resilience. I will also highlight ongoing clinical trials to evaluate the effects of bacteria with anti-inflammatory and immunoregulatory properties in United States Veterans with a diagnosis of PTSD.

Keynote 3

Martin Heni
University Ulm Medical Center, Ulm, Germany

Human glucose and energy metabolism are predominantly controlled by key peripheral organs, including the liver, pancreas, skeletal muscle, and adipose tissue. Recent research emphasizes these organs' interconnected functioning rather than individual actions. The brain appears to play a crucial role in coordinating these metabolic organs, a central pathway that is at least in part initiated through insulin action in the brain.

The peptide hormone insulin, well known for its role in peripheral metabolic organs, is also transported to the brain where it executes specific functions in distinct brain regions. By acting in the brain, insulin regulates satiety, eating behavior, and reward, and seems to influence memory processes.

Though, the hormone's actions in the brain are not only vital for brain processes, but also instrumental in modulating whole-body metabolism. Thereby, brain insulin action is crucially involved in modulating metabolic functions in the periphery. This mechanism is particularly critical after food intake, when the metabolic system must swiftly adapt to increased energy availability. Here, insulin action in the brain suppresses endogenous glucose production in the liver, promotes glucose uptake in skeletal muscle and adipose tissue, and stimulates endogenous insulin secretion from the pancreatic beta cells. Together, these processes collaborate to maintain metabolic homeostasis, adjusting energy fluxes to increased energy available following food intake.

However, not everyone responds similarly to insulin action in the brain. A substantial number of persons display diminished or even completely absent insulin action in the brain, a state often referred to as brain insulin resistance. This condition disrupts crucial regulatory signals from the brain to the periphery. It is associated with long-term weight gain, particularly in metabolically unfavorable areas like visceral adipose tissue (fat storage within the abdomen). Fat accumulation in this specific region significantly increases the risk of diabetes, cardiovascular diseases, and even certain cancers. Brain insulin resistance appears to be also a substantial risk factor for cognitive decline in elderly persons and might even contribute to neurodegenerative diseases.

First smaller studies in humans indicate that insulin resistance in the brain is not an immutable state. Exercise has shown to markedly enhance insulin action in the brain in otherwise sedentary individuals. In a recent pilot study, treatment with an SGLT2 inhibitor (an anti-diabetic drug) significantly enhanced insulin action in the hypothalamus in overweight individuals with prediabetes. Mediation analyses indicated that this improvement contributed to the metabolic benefits known for this drug class.

Therefore, it appears plausible to therapeutically target brain insulin resistance, potentially yielding favorable effects on systemic metabolism. Potential benefits of enhanced insulin action on brain processes, such as memory, are currently under investigation and represent an exciting frontier in this field.

Short oral presentations

OP01 Porcine blood cell and brain tissue energy metabolism: effects of "Early Life Stress

Nadja Carina Abele[1], Franziska Münz[2], Eva-Maria Wolfschmitt[1], Fabian Zink[1], Melanie Hogg[1], Andrea Hoffmann[1], Michael Gröger[1], Enrico Calzia[1], Christiane Waller[3], Peter Radermacher[1], Tamara Merz[2]

[1]Institute for Anesthesiological Pathophysiology and Process Engineering, Ulm University Medical Center, Germany; [2]Clinic for Anesthesiology and Intensive Care, Ulm University Medical Center, Germany; [3]Clinic for Psychosomatic Medicine and Psychotherapy, Paracelsus Medical Private University, Nuremberg, Germany

Background: Early Life Stress (ELS) may exert long-lasting biological effects, e.g. increased prevalence for neuropsychiatric and inflammation-associated disorders. Here, we investigated blood immune cell and brain tissue mitochondrial respiratory capacity in a porcine ELS model with a possible role of gender-specific differences.

Methods: ELS in German Large White Pigs (n=12) was induced by early weaning (postnatal day (PND) 21 (ELS) vs. PND 28-30 (control). PBMCs and granulocytes were isolated from whole blood and brain and heart were harvested immediately post mortem. Mitochondrial respiratory capacity of isolated cells and tissue homogenates was determined via high-resolution respirometry. ROS production from whole blood and isolated cells was estimated from superoxide O2•- detection via electron spin resonance. Immune cell radical production was determined before and after stimulating phagocytosis with E.coli particles. Blood plasma catecholamine concentrations were measured by LC/MS-MS.

Results: Mitochondrial respiratory capacity in the brain and immune cells did not differ with respect to group or gender. Higher radical production in granulocytes could be observed after phagocytosis for both genders, except for the female ELS group. Mitochondrial respiratory activity of peripheral blood immune cells and brain tissue did not correlate. Endogenous catecholamines were inversely related to cardiac mitochondrial respiratory capacity.

Conclusion: These results show, that i) mitochondrial capacity did not differ with exposure to ELS or with gender, ii) PBMCs cannot serve as a surrogate for tissue mitochondria iii) E.coli-stimulated ROS production was abolished in female ELS swine and iv) high endogenous catecholamine levels were associated with lower cardiac mitochondrial respiration.

OP02 Lactational stress influences milk composition but has little effect on stress responses of offspring in domestic pigs: Evidence for resilience?

Ulrike Gimsa[1], Ellen Kanitz[1], Margret Tuchscherer[1], Roberto Brückmann[2], Liza R. Moscovice[1]

[1]Research Institute for Farm Animal Biology (FBN), Germany; [2]EUROIMMUN AG, Germany

Background:

We tested whether stress to the mother during lactation affected subsequent development of the neuroendocrine and immune systems in offspring.

Methods:

Treated sows received adrenocorticotrophic hormone (ACTH) injections from lactational day (LD) 2 to 15, while control sows were injected with saline. Milk of ACTH-treated and control sows was tested over several LDs for cortisol, IgA, TGF-beta and TNF by ELISA. Plasma of offspring (n=200) was tested for cortisol early during lactation, and before and after two challenges: A maternal deprivation on day 20 either alone (DA) or with littermates (DG) and an ACTH injection on day 42. Innate immunity was tested by whole blood cell cultures with lipopolysaccharide (LPS) and analysis of TNF and IL-10 in supernatants by ELISA.

Results:

ACTH treatment increased milk cortisol across all lactation days. In addition, milk of ACTH-treated sows contained more IgA and less TGF-beta on LD 5 to 15. Piglets of ACTH-treated sows had higher plasma cortisol levels on LD 5 but not later on. ACTH treatment of the mothers did not influence the responses of piglets to maternal deprivation. Interestingly, cortisol increased in DA but not DG piglets, which indicates social buffering by littermates. Regardless of the treatment to their mothers, piglets responded similarly to an ACTH challenge with increased plasma cortisol and decreased IL-10 in LPS-stimulated cultures.

Conclusion:

Although lactational stress in sows changed milk composition, this did not influence the neuroendocrine responses of piglets to stress challenges early during their development, suggesting possible resilience to lactational programming effects.

OP03 The influence of everyday emotions on mucosal immunity: A multi-level structural equation modeling approach

Lennart Seizer[1], Johanna Gostner[2], Johanna Löchner[1]

[1]University of Tübingen, Germany; [2]Medical University Innsbruck, Austria

Mucosal immunity is a multifaceted system of immunological responses that provides a barrier against pathogenic invasion and can be regulated by psychosocial and neuroendocrine factors. The present study aims to elucidate the association between everyday emotional states, emotion regulation competences (ERC), and mucosal immunity by utilizing an ambulatory assessment approach. Thereby 30 healthy subjects completed an emotion questionnaire (PANAS) and collected saliva samples via passive drool to determine salivary immunoglobulin-A (S-IgA) levels three times a day over a period of one week (total = 630 samples). In a Bayesian multi-level structural equation model, the influence of emotions on S-IgA, both on a within-subject and between-subject level, was estimated. The study found that the variation in S-IgA secretion rate was mostly explained by within-subject variations (75%) rather than between-subject differences (25%). On a within-subject level, negative emotional states led to significant increases in S-IgA levels ($\beta = 0.41$, $p < .01$), while positive emotions had no effect. This effect of negative emotions was moderated by the subjects' ERC, with higher ERC corresponding to smaller effect sizes ($\beta = -0.33$, $p = .02$). Sampling time-of-day was negatively associated with S-IgA, indicating circadian rhythmicity ($\beta = -0.13$, $p < .01$). The estimated model explained about 27% of the variance in S-IgA on the within-subject level and 8% on the between-subject level. In conclusion, the results highlight the importance of ERC for understanding the immune effects of negative emotions and emphasize the possibilities of ambulatory assessment designs for further investigations in this field.

OP04 Psychological or inflammatory stimulation in mice: investigating how neutropenia affects heart rate variability as a readout parameter

Leona Bähr, Jessica Hernandez, Martin Feldotto, Doreen Marks, Joachim Roth, Christoph Rummel

Institute of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, Justus Liebig University Giessen

Stress affects the brain by immune cell trafficking, cytokines and the autonomous nervous system via neuronal signalling. Here, we investigated how psychological stress and systemic inflammation alter heart rate variability (HRV) in relation to changes in inflammatory markers in the brain and periphery in mice. We used HRV as a quantitative marker for autonomous nervous system activity providing some insights in terms of the sympathetic and parasympathetic tone.

Mice received an intraperitoneal injection with normal rabbit serum (NRS) as a control or an anti-polymorphnuclear neutrophil serum (anti-PMN) to deplete circulating neutrophil granulocytes by 30%. After 24h, mice underwent a novel environment stress test (NES) or not as a psychological stressor and control. In further experiments, we utilized PBS (phosphate buffered saline) or a low dose of LPS (50µg / kg) as an inflammatory stimulus. Using a telemetric implant, we continuously recorded HRV, body core temperature and locomotive activity throughout the experiment. Animals were perfused 24 hours after the LPS/PBS injection or 4 hours after the NES test and brain, pituitary, liver, spleen, retroperitoneal/inguinal fat, and blood were collected. This tissue and blood are going to be investigated regarding specific pro- and anti-inflammatory markers using bioassays, PCR, immunohistochemistry and Western Blot.

Our established experimental setup and the preliminary data from telemetric recordings show an effect of LPS that could be exacerbated by PMN, which would indicate a decrease of HRV. New insights into the role of neutrophils regarding the autonomous regulation are currently assessed.

OP05 Immune signature of multiple sclerosis-associated depression

Jelena Brasanac[1], Caren Ramien[2], Stefanie Gamradt[1], Aline Taenzer[1], Laura Glau[2], Kristin Ritter[1], Kostas Patas[3], Agorastos Agorastos[4], Klaus Wiedemann[2], Cüneyt Demiralay[2], Felix Fischer[1], Christian Otte[1], Judith Bellmann-Strobl[1], Manuel Friese[2], Eva Tolosa[2], Friedemann Paul[1], Christoph Heesen[2], Martin Weygandt[1], Stefan Gold[1]

[1]Charite Universitätsmedizin Berlin, Germany; [2]Universitätsklinikum Hamburg-Eppendorf, Germany; [3]Eginition University Hospital, Greece; [4]Aristotle University of Thessaloniki, Greece

Background: Multiple neurobiological pathways have been implicated in the pathobiology of major depressive disorder (MDD). The identification of reliable biological substrates across the entire MDD spectrum, however, is hampered by a vast heterogeneity in the clinical presentation, presumably as a consequence of heterogeneous pathobiology. One way to overcome this limitation could be to explore disease subtypes based on biological similarity such as "inflammatory depression". As such a subtype may be particularly enriched in depressed patients with an underlying inflammatory condition, multiple sclerosis (MS) could provide an informative disease context for this approach. Few studies have explored immune markers of MS-associated depression and replications are missing.

Methods: We analysed flow cytometry data from two independent case-control studies on immune signatures of MS-associated depression, conducted at two different academic MS centers with an overall sample size of n = 132.

Results: Using a stepwise data-driven approach, we identified CD4+CCR7lowTCM cell frequencies as a robust correlate of depression in MS. This signature was associated with core symptoms of depression and depression severity (but not MS severity per se) and linked to neuroinflammation as determined by magnetic resonance imaging (MRI). Furthermore, exploratory analyses of T cell polarization revealed this was largely driven by cells with a TH1-like phenotype.

Conclusion: Our findings suggest (neuro)immune pathways linked to affective symptoms of autoimmune disorders such as MS, with potential relevance for the understanding of "inflammatory" subtypes of depression.

OP06 Characterisation of Circulating Dendritic Cells in Major Depressive Disorder

Anna-Lena Boller[1,2], Jana Freff[1,2], Kathrin Schwarte[1], Rafael Leite Dantas[1,2], Volker Arolt[3], Udo Dannlowski[3], Bernhard T. Baune[1,4,5], Stefanie Scheu[6], Judith Alferink[1,2]

[1]Department of Mental Health, University of Münster, Münster, Germany; [2]Cells in Motion Interfaculty Centre, University of Münster, 48149 Münster, Germany; [3]Institute for Translational Psychiatry, University of Münster, Münster, Germany; [4]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Australia; [5]Department of Psychiatry, The University of Melbourne, Melbourne, Australia; [6]Institute of Medical Microbiology and Hospital Hygiene, University of Düsseldorf, Düsseldorf, Germany

Background: Major depressive disorder (MDD) is a severe mental disorder associated with alterations of the innate immune system. Childhood trauma (CT) is a risk factor for development of MDD in adulthood. Plasmacytoid dendritic cells (pDCs) are a subset of DCs highly capable of antiviral responses via production of type 1 interferons (IFN-I). In this study, we investigated the impact of CT on pDC frequencies and IFN-α levels in peripheral blood in individuals with MDD and healthy controls (HC) and their predictive capacity for disease severity.

Methods: PDC frequencies and IFN-α concentrations were assessed using multi-parameter flow cytometry and multiplex assays of blood samples from depressed individuals (n=63) and HC (n=37). Each group included individuals with CT. Using stratification for MDD and/or CT severity as well as correlational analysis, we examined the associations with immune parameters. Additionally, we performed multivariate linear regression to assess their predictive capacity for disease severity.

Results: Equivalent frequencies of pDCs were found in MDD and HC. Stratification, however, revealed a reduction of pDCs exclusively in severe MDD or severe CT. Specifically, a negative correlation between pDC frequencies and physical or sexual abuse, and CTQ sum score was found. Importantly, blood pDC proportions and IFN-α levels were significant predictors of severity of depression.

Conclusion: This study defines specific changes of pDCs and IFN-α in MDD and individuals with CT and their predictive capacity for disease severity. This novel immune signature suggests an association of pDC blood frequencies and their effector cytokine with the pathophysiology of depression.

OP07 The circadian system, sleep, and platelets in healthy individuals and in patients with systemic sclerosis

Tanja Lange[1], Hanna Graßhoff[1], Sarah Stenger[1], Finn Luebber[1], Stoyan Dimitrov[2], Luciana Besedovsky[3], Sabine Sommerlatte[4], Gabriela Riemekasten[1]

[1]University of Lübeck, Germany; [2]University of Tübingen, Germany; [3]Ludwig-Maximilians-Universität München, Germany; [4]Martin Luther University Halle-Wittenberg, Germany

Background: Platelet markers in blood like platelet counts and volume (mean platelet volume, MPV) are influenced by stress mediators and altered in inflammatory conditions. Disturbances of the sleep-wake cycle lead to changes in stress and immune parameters. However, the interplay between the circadian system, sleep, and platelets is understudied. Methods: To monitor acute changes in platelets during the sleep-wake cycle, we sampled blood repeatedly for 24 hours in 15 healthy individuals on two occasions, once with regular sleep from 11 PM to 7 AM, once during a period of continuous wakefulness. To assess disturbances of the circadian system, sleep, and platelets in the autoimmune disease systemic sclerosis (SSc), we characterized 33 patients with respect to chronotype and social jetlag, sleep quality, sleepiness, and fatigue, and sampled blood once before noon. In both studies we measured platelet counts and MPV. Findings: In healthy controls platelet counts continuously decreased during nocturnal sleep with lower values at 6:30 AM compared to the condition of continuous wakefulness. Likewise, MPV dropped at night reaching minimum levels at 2 AM with no differences between conditions of sleep and continuous wakefulness. In SSc patients platelet counts showed positive associations with social jetlag, but negative associations with sleepiness and fatigue. We found no associations of platelet counts with chronotype or sleep quality and no associations between self reports and MPV. In sum, there are complex effects of the circadian system and sleep on platelets, in particular in SSc patients.

OP08 Circadian influences in a mouse model of autoimmune skin blistering disease

Sarah Stenger[1], Rebecca Pfündl[1], Tasja Romina Stilla[1], Veronika Hartmann[1], Christiane Koch[5], Henrik Oster[2], Tanja Lange[2,3], Jennifer Hundt[1,4]

[1]Lübeck Institute of Experimental Dermatology, University of Lübeck, Germany; [2]Center of Brain, Behavior and Metabolism (CBBM), University of Lübeck, Germany; [3]Department of Rheumatology and Clinical Immunology, University of Lübeck, Germany; [4]Center for Research on Inflammation of the Skin, University of Lübeck, Germany; [5]University Hospital Ulm, Germany

Introduction:

The circadian system is known to control various processes throughout the body in health and disease. We aimed to investigate circadian influences on the progression and development of the autoimmune skin blistering disease epidermolysis bullosa acquisita (EBA).

Methods:

EBA was induced in mice by injecting an antibody directed against murine type VII collagen (mCOL7c) at the beginning of the rest (7 AM) or the activity period (7 PM). We compared the disease scores of affected skin areas at day 4, 8 and 12.

Results:

In male C57BL/6 mice, AM vs PM injection induced higher disease scores. To confirm that these differences were due to intrinsic clocks, the experiments were performed again in male and female Per1/2 knockout mice compared to C57BL/6 mice. Here, female compared to male C57BL/6 mice showed higher disease scores following PM, but not following AM injection. There were no sex differences in Per1/2 knockout mice. When comparing AM vs PM injection diseases scores tended to be higher in male C57BL/6 mice (confirming our previous findings), but lower in female C57BL/6 mice. This reversed pattern was not evident in Per1/2 knockout mice.

Discussion:

The time point of mCOL7c injection impacts EBA disease scores, when sex is taken into account. The complex interactions between AM vs PM injection and sex on affected skin areas disappear in Per1/2 knockout mice, which supports the assumption that these effects are driven by intrinsic clocks and not only by external time cues.

OP09 Alterations of DNA Repair in Immune Cells of Patients with Posttraumatic Stress Disorder and Their Relation to Genomic Integrity and Traumatic Stress

Matthias Mack[1,2], Alexander Behnke[1], Judy Fieres[2], Markus Christmann[3], Alexander Bürkle[2], María Moreno-Villanueva[2,4], Iris-Tatjana Kolassa[1]

[1]Clinical and Biological Psychology, Institute of Psychology and Education, Ulm University, Albert-Einstein-Allee 47, 89081, Ulm, Germany; [2]Molecular Toxicology, Department of Biology, University of Konstanz, 78457, Constance, Germany; [3]Applied Toxicology, Institute of Toxicology, University of Mainz, 55131, Mainz, Germany; [4]Department of Sport Science, Human Performance Research Centre, University of Konstanz, 78457, Constance, Germany

Background: Traumatic stress has been shown to increase oxidative stress and compromise genomic integrity. Previous research has found elevated DNA damage in immune cells of posttraumatic stress disorder (PTSD) patients. We aimed to investigate whether the induction of cellular DNA repair capacity with functional changes in DNA-repair kinetics is necessary for maintaining genomic integrity in PTSD.

Methods: We conducted semi-quantitative polymerase-chain reaction of DNA-repair genes (X-ray repair cross complementing 1 [XRCC1], poly [ADP-ribose] polymerase 1 [PARP1], and polymerase β [Polβ]) as well as Fluorometric Detection of Alkaline DNA Unwinding after ex vivo induction of DNA damage to assess gene expression and their functional relevance for DNA repair in immune cells. The study included 14 individuals with PTSD and 15 controls.

Results: We found significantly higher XRCC1 expression in immune cells of PTSD patients compared to controls ($U=161.0$, $p=0.009$, Cohen's $r=0.49$), and positive correlations between the severity of PTSD symptoms and the expression of both XRCC1 ($rS=0.57$, $p=0.002$) and PARP1 ($rS=0.43$, $p=0.022$). Moreover, higher XRCC1 ($F=2.39$, $p=0.010$, $\eta 2p=0.10$) and PARP1 ($F=2.15$, $p=0.022$, $\eta 2p=0.09$) expression was associated with slower repair of experimentally induced X-ray irradiation-induced DNA damage.

Conclusion: Our findings suggest that PTSD involves increased oxidative stress and DNA damage in immune cells, and that compensatory regulation of DNA-repair mechanisms, such as the increased expression of XRCC1 and PARP1, is required to achieve a physiologically tolerable equilibrium between DNA damage and repair. These results may have implications for cellular senescence, premature aging, and physical morbidity in PTSD patients.

OP10 Omega-3 polyunsaturated fatty acids modulate the lung-brain axis of communication during LPS-induced ARDS

Julia Schaeffer[1], Jessica Hernandez[2], Christiane Herden[2], Fabian J. Pflieger[2], Sylvia Reiche[1], Hiromu Kitagawa[3], Joelle Welter[2], Carsten Culmsee[4], Jens Bier[1], Natascha Sommer[1], Jing X. Kang[5], Konstantin Mayer[6], Matthias Hecker[1], Christoph Rummel[2]

[1]Cardio-Pulmonary Institute, Justus Liebig University, Giessen, Germany; [2]Institute of Veterinary Physiology and Biochemistry Justus Liebig University Giessen, Germany; [3]Institute of Veterinary Pathology Justus Liebig University Giessen, Germany; [4]Institute of Pharmacology and Clinical Pharmacy, Philipps University of Marburg, Marburg, Germany; [5]Laboratory for Lipid Medicine and Technology, Department of Medicine, Massachusetts General Hospital and Harvard Medical, Charlestown, United States; [6]Department of Internal Medicine, Justus Liebig University, Giessen, Germany

Background: Omega-3 polyunsaturated fatty acids (n-3 PUFAs) and its derivatives like resolvin (Rv) E1 can resolve inflammation during lung diseases like acute respiratory distress syndrome (ARDS). ARDS is characterized by a rapid and widespread inflammation in the lung, nevertheless many ARDS patients show neurocognitive impairments as well.

Methods: To analyze the connection between lung and brain, ARDS was induced in transgenic mice by intratracheal application of lipopolysaccharide (LPS, 10µg). To investigate the therapeutic potential of n-3 PUFAs during ARDS, genetically n-3 PUFA enriched Fat-1 mice were used and crossbred with RvE1 receptor knockout mice. Mice were sacrificed at 0h, 4h, 24h, 72h and 120h post inflammation. RT-PCR, multiplex, immunohistochemistry, western blot and LC-MS/MS analysis were used to determined effects on lung, liver and brain.

Results: LPS-induced lung inflammation increased inflammatory signaling not only in the lung but also in the periphery and in the hypothalamus as revealed by protein and mRNA analyzes. LC-MS/MS analysis demonstrated modified n-3 PUFAs levels in lung and brain mostly due to genetic enrichment of n-3 PUFAs in Fat-1 mice. Moreover, neutrophil recruitment in different brain structures was altered with genetic enrichment of n-3 PUFAs in Fat-1 mice and by RvE1 receptor deficiency.

Conclusion: Overall, during ARDS, the humoral pathway and immune cell trafficking to the brain contributed to immune-to-brain communication. Genetic enrichment of n-3 PUFAs in Fat-1 mice as well as deficiency in RvE1 receptors effects lung-brain interaction during ARDS by altering profiles of several inflammatory markers and lipid mediators.

OP11 Daily pet contact during urban upbringing ameliorates the inflammatory stress-response during adulthood

Dominik Langgartner[1,4], Katja Weimer[2,4], Jonas Brunner-Weisser[1], Raphael Winkler[1], Nicolas Rohleder[3], Marc N. Jarczok[2], Harald Gündel[2], Stefan O. Reber[1]

[1]Laboratory for Molecular Psychosomatics, Department of Psychosomatic Medicine and Psychotherapy, Ulm University Medical Center, 89081 Ulm, Germany; [2]Department of Psychosomatic Medicine and Psychotherapy, Ulm University Medical Center, 89081 Ulm, Germany; [3]Chair of Health Psychology, Department of Psychology, Friedrich-Alexander-University, Erlangen-Nürnberg, 91054 Erlangen, Germany; [4]these authors contributed equally

Individuals raised in an urban environment (URBANs) in the absence of pets show an exaggerated inflammatory stress-response compared with individuals raised in a rural environment with regular animal contact. In the current study we recruited young, physically and emotionally healthy male URBANs, raised in a city with more than 40,000 residents either in the absence or presence of own pets during five out of the first ten years of life. Participants were individually exposed to the TSST and before and after the TSST, blood was drawn for assessment of plasma physiological and immunological measures. Mental and physical health status, early life and perceived life stress, and subjective strain induced by TSST exposure were assessed using validated questionnaires. Here we report that healthy male URBANs raised in the absence vs. presence of pets showed a prolonged increase in the number of blood leukocyte counts, in particular of lymphocytes and neutrophil granulocytes, in response to acute psychosocial stress induced by the Trier social stress test (TSST). Moreover, plasma and ex vivo peripheral blood mononuclear cells (PBMCs)-derived secretion of proinflammatory interleukin (IL)-6 in response to the TSST were higher in URBANs raised in the absence vs. presence of pets, while respective measures for antiinflammatory IL-10 were lower. Together, our findings support the hypothesis that the presence of pets during urban upbringing reduces the risk to develop stress-associated disorders later in life by abrogating immunoregulatory deficits and, consequently, normalizing stress-induced immune activation.

OP12 Deciphering neuroprotective effects of n-3 polyunsaturated fatty acids and related impacts of adipokines using organotypic hippocampal slice and primary neuroglial cell cultures

Martin Feldotto[1], Daniela Ott[1], Carsten Culmsee[2,3], Jessica Hernandez[1], Mary Slayo[4], Sarah J. Spencer[4], Christoph Rummel[1,3]

[1]Institute of Veterinary Physiology and Biochemistry, Justus Liebig University Giessen, Germany; [2]Institute of Pharmacology and Clinical Pharmacy, Philipps University of Marburg, Germany; [3]Center for Mind Brain and Behavior, Universities Giessen and Marburg, Marburg, Germany; [4]School of Health and Biomedical Sciences, RMIT University, Bundoora, Melbourne, VIC, Australia

Alzheimer's disease (AD) is characterised by amyloid-beta (Aβ) and tau neuropathology and progressive, debilitating cognitive decline. Early life stress leads to brain inflammation, changes in lipid mediators in AD and exacerbates amyloid pathology. Recent studies have shown that specialized pro-resolving lipid mediators (SPMs, derivatives of omega-3 polyunsaturated fatty acids, n-3) and metabolic sensors such as adipokines affect AD disease states.

The aim of the present study is to decipher neuroprotective properties of n-3 and their metabolites (SPMs) and how this effect is modulated by adipokines like C1q/TNF-Related Protein 3 (CTRP3). For this purpose, we use organotypic hippocampal slice cultures (slices) from male and female neonatal mice exposed to early stress and incubate them with Aβ oligomer-enriched stocks. Here, we present the project methodology of our established slice cultures and first results after excitotoxic or inflammatory stimulation with either NMDA and glutamate or bacterial lipopolysaccharide (LPS). Moreover, we show that LPS increases SPMs release and CTRP3 inhibited LPS-induced IL-6 secretion in primary neuroglial cell cultures. We are further testing if stimulation of the slices in the way described above leads to changes in neuronal survival using propidium iodide, detection of inflammatory signalling (RT-PCR) and measures of cytokines/PUFAs/SPMs. To reveal the functional role of resolvin E1 (RevE1), we will also derive slices from Fat1-mice that lack resolvin receptors (ChemR23-deficiency), to model n-3 enrichment with and without functional RevE1-signalling. As a positive pharmacological control, slices from wild-type mice will be treated with either 18-HEPE, the direct precursor for RevE1, or RevE1 directly.

OP13 Mycobacterium vaccae ATCC 15483 immunization as an intervention for Western diet-induced physiological and behavioral changes in adolescent male mice

Luke Desmond[1], Evan Holbrook[1], Tyler Akonom[1], Lamya'a Dawud[1,5], Brandon Marquart[1], Elizabeth Hunter[1,2], Lyanna Kessler[1], Nathan Andersen[1], Dennis Boateng[1], Lucas Guerrero[1], Christopher Lowry[3,4,6,7,8]

[1]Department of Integrative Physiology, University of Colorado Boulder, Boulder, CO 80309, USA; [2]Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, CO 80309, USA; [3]Center for Neuroscience, University of Colorado Boulder, Boulder, CO 80309, USA; [4]Center for Microbial Exploration, University of Colorado Boulder, Boulder, CO 80309, USA; [5]f Sleep and Metabolism Laboratory, Department of Health and Exercise Science, Colorado State University, Fort Collins, CO, USA; [6]Department of Physical Medicine and Rehabilitation, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA; [7]Center for Neuroscience, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA; [8]Veterans Health Administration, Rocky Mountain Mental Illness Research Education and Clinical Center (MIRECC), The Rocky Mountain Regional Veterans Affairs Medical Center (RMRVAMC), Aurora, CO 80045, USA

Background: Inflammation, obesity, and the prevalence of stress-related psychiatric disorders are increasing in modern urban societies. A possible explanation for the rise of inflammation in modern urban societies is the lack of exposure to certain immunoregulatory microbes, “Old Friends,” that humans have coevolved with. In this study we investigated the effects of an “Old Friend”, Mycobacterium vaccae ATCC 15483 on “Western-style” diet-induced weight gain, adiposity, neuroinflammation, and behavior in male mice.

Methods: Mice were randomly divided into either treatment with M. vaccae ATCC 15483 (s.c., 0.1 mg in 0.1 ml sterile borate-buffered saline vehicle, weekly starting on day –77 and ending on day –7) or vehicle. Within these groups, mice were provided with either a Western diet or a control diet, resulting in a 2 x 2 design with n = 12 mice per group. Mice were assessed in the elevated plus-maze (EPM) day 3 and euthanized on day 4 collection of tissues and assessment.

Results: Exposure to a Western diet resulted in an increase in anxiety-like behavior in the EPM as well as increases in body weight gain and visceral adiposity. Immunization with M. vaccae ATCC 15483 prevented Western diet-induced body weight gain and visceral adiposity without significantly altering calorie or water consumption. In addition, M. vaccae ATCC 15483 had a main effect to decrease anxiety-like defensive behavioral responses in the EPM.

Conclusions: Results support the hypothesis that M. vaccae ATCC 15483 has potential for protection against adverse outcomes associated with exposure to a Western diet in male mice.

OP14 Effects of Mycobacterium vaccae ATCC 15483 on biobehavioral health outcomes following a "two-hit" model of chronic disruption of rhythms and a Western diet in male and female C57BL/6N mice

Lamya'a M. Dawud[1,2], Brandon M. Marquart[1], Luke Desmond[1], Nathan D. Andersen[1], Saydie A. Sago[1], Matthew G. Frank[1,10], Lyanna R. Kessler[1], Haoting Zhang[1], Elizabeth AH Hunter[1], Richard N. Zabat[1], Aislinn E. Concha[1], Miguel A. Espino[1], Mackenzie G. Johnson[1], Annie E.Z. O'Brien[1], Adam M. Kulakowski[1], John D. Sterrett[1,7], Matthew J. Gebert[3,4,5], Josiane L. Broussard[2,6], Christopher A. Lowry[1,8,9,11]

[1]Department of Integrative Physiology, University of Colorado Boulder, Boulder, CO 80309, USA; [2]Sleep and Metabolism Laboratory, Department of Health and Exercise Science, Colorado State University, Fort Collins, CO, USA; [3]Department of Ecology and Evolutionary Biology, University of Colorado Boulder, Boulder, CO 80309, USA; [4]Center for Microbial Exploration, University of Colorado Boulder, Boulder, CO 80309, USA; [5]Cooperative Institute for Research in Environmental Sciences, University of Colorado Boulder, CIRES Bldg. Rm. 318, Boulder, CO 80309, USA; [6]Division of Endocrinology, Diabetes, and Metabolism, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [7]BioFrontiers Institute, University of Colorado Boulder; [8]Center for Neuroscience, University of Colorado Boulder, Boulder, CO 80309, USA; [9]Department of Physical Medicine and Rehabilitation and Center for Neuroscience, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA; [10]Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, CO 80309, USA; [11]Veterans Health Administration, Rocky Mountain Mental Illness Research Education and Clinical Center (MIRECC), Rocky Mountain Regional Veterans Affairs Medical Center (RMRVAMC), Aurora, CO 80045, USA

Chronic disruption of rhythms (CDR) and consumption of a Western high-fat/high-sugar diet (WD) both induce systemic inflammation, a risk factor for the development of stress-related psychiatric disorders. In contrast, Mycobacterium vaccae ATCC 15483 is a bacterium that can ameliorate stress-induced systemic and neuroinflammation, as well as mitigate the negative behavioral consequences of acute and chronic stress exposures. However, it is unclear whether M. vaccae can prevent the biobehavioral health impairments associated with the combined disruption of biological rhythms and diet. We therefore tested the hypothesis that immunization with a whole-cell, heat-killed preparation of M. vaccae ATCC 15483 prior to and during a "two-hit" stressor model that simultaneously pairs a WD with CDR prevents negative biobehavioral health outcomes. Eight-week-old male and female mice received weekly injections of a whole-cell, heat-killed preparation of M. vaccae ATCC 15483 (0.1 mg s.c.; 1 x 108 bacteria, days –21 to 49) or vehicle. On day 0, mice were assigned to either a continuous regular diet (RD) or WD and either a normal light:dark condition (NLD) or CDR condition for eight weeks. Mice were then tested in object location memory test (day 53), open-field test (day 54), and elevated plus-maze test (day 55). Although WD and CDR had no effects on behavior, treatment with M. vaccae ATCC 15483 prevented WD-induced increases in adiposity in male mice. These data are consistent with the hypothesis that a "two-hit" stressor of WD/CDR has sex-specific effects on biobehavioral outcomes that can be prevented by immunization with M. vaccae ATCC 15483.

OP15 Interplay of inflammation and negative mood on visceral pain perception - A randomized controlled fMRI trial in healthy volunteers

Sven Benson[1], Franziska Labrenz[2], Simone Kotulla[1], Lisa Brotte[1], Phillipp Rödder[1], Bastian Tebbe[1], Nina Theysohn[1], Harald Engler[1], Sigrid Elsenbruch[2]

[1]University Hospital Essen, Germany; [2]Ruhr-University Bochum, Germany

Background: Inflammation and depressed mood constitute clinically relevant vulnerability factors for interoceptive pain, but their putative interaction remains untested in humans. We combined experimental endotoxemia and a mood induction paradigm to test interaction effects of acute systemic inflammation and sad mood on the anticipation and experience of visceral pain.

Methods: We performed a double-blind, placebo-controlled, crossover fMRI-trial in N=39 healthy volunteers, involving 2 study days with i.v. administration of 0.4ng/kg lipopolysaccharide (LPS; inflammation condition) or saline (control). Scanning sessions were conducted in a sad and a neutral mood condition on both study days. Pain unpleasantness was assessed with Visual Analogue Scales. In all sessions, identical individually-calibrated painful rectal distensions were implemented, signaled by predictive visual cues to assess pain anticipation. All analyses accounted for sex as covariate.

Results: LPS administration led to transient, significant increases in TNF-α, IL-6, and sickness symptoms. The mood paradigm effectively induced distinct mood states, with greater sadness in the negative mood conditions. Significant main and interaction effects of inflammation and negative mood were observed for pain unpleasantness. During cued pain anticipation, a significant inflammation X mood interaction emerged for the bilateral caudate nucleus and right hippocampus. Main effects of both inflammation and mood were observed in multiple brain regions.

Conclusions: Results support an interplay of inflammation and sad mood on striatal and hippocampal circuitry engaged during visceral pain anticipation as well as on pain experience. This may reflect a nocebo mechanism, which contributes to altered perception and interpretation of bodily signals, amplifying visceral pain experience.

OP16 Autoantibodies Against Surface Molecules are Altered in Fibromyalgia Syndrome

Finn Luebber[1], Johanna Strobach[1], Frieder M. Paulus[1], Harald Heidecke[2], Hanna Graßhoff[1], Tanja Lange[1], Gabriela Riemekasten[1]

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

Background

Fibromyalgia syndrome (FMS) is a disease mainly characterized by long lasting and widespread pain, the etiology of which is incompletely understood. Recently, it has been suggested that FMS has an autoimmune component involving autoantibodies.

Methods

In n = 146 participants (91 with primary FMS (pFMS), 24 with secondary FMS (sFMS), 31 healthy controls (HC)) we analyzed autoantibody levels against 27 surface molecules using solid-phase sandwich enzyme-linked immunosorbent assays (ELISA) and assessed demographic variables and symptom load using questionnaires.

Results

We found levels of autoantibodies that were different between pFMS and sFMS patients and HC. Together the levels of autoantibodies were able to discriminate between pFMS patients and HC to a modest degree. Antibodies against angiotensin converting enzyme (ACE)2 were most robustly altered and contributed most to predictive accuracy. Additionally, we found that autoantibody levels were all positively correlated but clustered into two groups. Correlation of autoantibody levels and pain symptoms were weak and non-significant in pFMS and HC, however there were negative correlations in the sFMS group.

Conclusion

These results provide first evidence that autoantibody concentrations and their joint regulation are altered in FMS compared to HC. The small effect size and impact of confounding lifestyle and demographic variables indicate that further research is needed to robustly corroborate the autoimmune disease hypothesis and establish autoantibodies in diagnostic routines of FMS. Here, a broader model of the causal relationships of variables involved in FMS will be necessary to gain insights from non-experimental studies.

OP17 Neuropenia exaggerates the inflammatory response in the brain and periphery during LPS-induced severe systemic inflammation

Jessica Hernandez[1], Fabian Pflieger[1], Jenny Schneiders[1], Karsten Krüger[2], Thomas Reichel[2], Christoph Rummel[1]

[1]Institute of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, Justus-Liebig University Giessen; [2]Institute of Sports Science, Department of Exercise Physiology and Sports Therapy, Justus Liebig University Giessen

The innate immune system plays a pivotal role in shaping acute inflammatory and sickness responses, such as thermoregulation, through immune-to-brain signaling. Previous studies have shown that leukopenia can alter sickness responses resulting in prolonged fever. Moreover, neutropenic fever is a severe clinical status of unknown origin. Here, we aimed to investigate the effects of neutropenia on the sickness response and immune-to-brain signaling during acute systemic inflammation in mice. To induce neutropenia and systemic inflammation, mice received an intraperitoneal injection of anti-polymorphonuclear serum (PMN) followed by a high dose intraperitoneal injection of lipopolysaccharide (LPS, 2.5 mg/kg) 24h later. Brains, peripheral tissue, and serum were collected at 4h or 24h after LPS-stimulation for detection of peripheral/brain inflammatory markers. To investigate the physiological significance of neutropenia, we continuously recorded locomotor activity, core body temperature, food, and water intake using a telemetric system. Compared to control mice PMN-pretreatment alone caused a reduction in body weights and in combination with LPS lead to a 20% reduction in circulating neutrophil granulocytes (NG) and inhibited recruitment of NGs to the brain. LPS-induced hypothermia was exacerbated in mice that received PMN (24h) while physiological parameters remained unaffected. Further analyses revealed that LPS-induced corticosterone levels in serum were altered (4h and 24h) and circulating cytokines were elevated (4h and 24h) in PMN mice. In the hypothalamus, several key mediators of inflammation were enhanced by PMN-pretreatment (24h). Together, our ongoing experiments suggest an anti-inflammatory role of NG with neutropenia exacerbating sickness and immune responses during systemic inflammation.

OP18 Treatment expectation effects on inflammation-induced bodily sickness symptoms and mood disturbances in human experimental endotoxemia

Justine Schmidt[1,2], Johanna Reinold[1,3], Sigrid Elsenbruch[4,5], Oliver Witzke[3], Manfred Schedlowski[1], Harald Engler[1], Sven Benson[1,2]

[1]Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, Center for Translational and Behavioral Neuroscience (C-TNBS), University Hospital Essen; [2]Institute for Medical Education, University Hospital Essen, Center for Translational and Behavioral Neuroscience (C-TNBS), University Hospital Essen; [3]Department of Infectious Diseases, University Hospital Essen; [4]Department of Medical Psychology and Medical Sociology, Faculty of Medicine, Ruhr University Bochum; [5]Department of Neurology, University Hospital Essen, Center for Translational and Behavioral Neuroscience (C-TNBS), University Hospital Essen

Background: Inflammatory mediators released during inflammatory conditions induce unspecific physical and psychological sickness symptoms. It remains unclear whether sickness symptoms can be modulated by treatment expectations. We employed the experimental endotoxemia model to induce sickness symptoms in healthy volunteers in combination with a placebo-controlled anti-inflammatory drug treatment, aiming to test for treatment expectation effects on inflammation-mediated sickness symptoms.

Methods: All healthy volunteers received 0.8ng/kg lipopolysaccharide (LPS) to induce sickness symptoms. In randomized, double-blind manner, LPS-injection was preceded by oral intake of an active anti-inflammatory drug (ibuprofen) or a placebo, which was combined with positive or neutral treatment-related information. We herein report on data from the placebo arm (N=62) of this ongoing study. Subjective sickness symptoms and inflammatory markers were repeatedly assessed up to six hours post LPS-injection.

Results: LPS application induced transient increases in inflammatory markers and self-reported sickness symptoms in all participants (all $p<.001$, time effect). Compared to neutral treatment expectation, participants in the positive condition reported significantly less bodily symptoms during the peak of inflammation ($p<.01$). Additionally, exploratory analyses indicated less mood disturbances (i.e. decreased dysthymia) during LPS-induced inflammation after induction of positive treatment-related expectations.

Conclusion: Our findings indicate a beneficial effect of verbally induced positive expectations on sickness symptoms, suggesting that positive treatment-related expectations may enhance treatment efficacy in the context of immune-mediated sickness symptoms. As LPS induced a comparable peripheral immune response in both groups, it is conceivable that expectation effects are mediated via inhibitory central pathways but further research is needed to elucidate underlying mechanisms.

OP19 Fatigue assessed by FACIT-F subscale correlates with patients' perception of symptom severity in psoriatic arthritis

Hanna Grasshoff[1,2], Sara Comdühr[1], Moritz Jägemann[1], Tanja Lange[1], Gabriela Riemekasten[1], Diamant Thaçi[2], Peter Lamprecht[1,2]

[1]Department of Rheumatology and Clinical Immunology, University of Lübeck, Lübeck, Germany; [2]Comprehensive Center for Inflammation Medicine, University Medical Center Schleswig-Holstein (UKSH), Lübeck, Germany

Background

Fatigue is a frequent symptom defined by prolonged periods of exhaustion leading to severe individual and socioeconomic consequences. However, fatigue is insufficiently considered in clinical praxis and in remission criteria. The aim of this study is to investigate the impact of fatigue on patients' perception of disease.

Methods

In 81 participants with psoriatic arthritis with an indication for systemic therapy according to international guidelines (baseline), disease activity was assessed using PASI, DAS28-CRP, 68 tender and 66 swollen joint count (tjc, sjc). Itch, pain, patient and physician global disease activity (gda) were reported on visual analogue scales. Fatigue was assessed using FACIT-F subscale. In 48 patients remission was assessed at week 16 using Minimal Disease Activity (MDA) criteria.

Results

In the respective cohort 40 of 81 (49.4%) patients reported fatigue at baseline. At treatment initiation Spearman correlation analyses revealed significant correlations between FACIT-F subscale and itch ($r=-0.2987$, $p=0.0097$), pain ($r=-0.04341$, $p<0.0001$) as well as patient gda ($r=-0.4351$, $p=0.0009$). No significant correlations were found with PASI ($r=0.1875$, $p=0.094$), tjc ($r=-0.2364$, $p=0.0621$), sjc ($r=-0.0023$, $p=0.9857$), physician gda ($r=-0.1064$, $p=0.4576$) and DAS28-CRP ($r=0.0635$, $p=-0.2411$). FACIT-F subscale improved between baseline and week 16 (Wilcoxon matched-pairs signed rank test; $p=0.019$). Binomial logistic regression analysis revealed an association between FACIT-F subscale at baseline and treatment response according to MDA criteria ($R2McF=0.0676$, $p=0.027$).

Conclusion

These results indicate an impact of fatigue on patients' perception of disease activity and support the need for objective assessments of fatigue.

OP20 Induction of negative treatment expectation in an animal model of endotoxin-induced sickness

Kirsten Dombrowski, Lisa Trautmann, Sebastian Wenzlaff, Manfred Schedlowski, Harald Engler

Institute of Medical Psychology and Behavioral Immunobiology, Center for Translational and Behavioral Neurosciences (C-TNBS), University Hospital Essen, University of Duisburg-Essen, Essen, Germany

Background: Despite broad clinical implications, the neurobiological underpinnings of negative treatment expectation are largely unknown. For ethical reasons, such mechanistic insights are difficult to obtain in humans. This calls for translational studies in animals mimicking clinically relevant features of negative treatment expectation. Here we present initial results from an animal model of endotoxin-induced sickness aiming to induce negative treatment expectation in rats.

Methods: Using a conditioned taste avoidance (CTA) paradigm, we combined the presentation of an unfamiliar bitter-sweet taste (saccharin) via the drinking water with the injection of bacterial endotoxin (lipopolysaccharide) as sickness-inducing agent. This was done for up to three times, to vary the amount of learning experiences. After a consolidation phase of six days, animals were re-exposed to the taste stimulus alone, and the consumed amount of saccharin solution was quantified as a measure of the CTA. Additionally, plasma stress hormone levels and expression of neural activation markers (c-fos, arc) in key regions of the central fear network were assessed.

Results: Conditioned animals developed a pronounced CTA that was significantly greater in individuals with more learning trials. Moreover, re-exposure to the taste stimulus induced a conditioned increase in plasma corticosterone levels. Brain analyses are ongoing.

Conclusions: Our preliminary findings show successful induction of a negative treatment expectation as well as a conditioned stress response, which both were strongly correlated with the number of prior treatment experiences.

OP21 Hypoxia priming aggravates LPS induced systemic inflammatory response in vivo in humans

Marie Jakobs[1], Anna Lena Friedel[1], Bastian Tebbe[2], Tina Schönberger[2], Joachim Fandrey[2], Manfred Schedlowski[1], Tina Hörbelt-Grünheidt[1]

[1]Institute of Medical Psychology and Behavioral Immunobiology, University Medicine Essen, Germany; [2]Institute of Physiology, University Medicine Essen, Germany

Background: A controlled activation of immune cells is crucial for the human immune defense and impaired in several diseases. LPS and hypoxia are regulators of immune cell activation and function controlling inflammatory responses. However, the impact of hypoxia on LPS driven inflammatory processes in humans is not known so far. Therefore, the current study aimed at investigating the effect of hypoxic conditions prior to LPS administration on physiological and immunological parameters in humans.

Methods: 30 healthy men were recruited (21-33 years) and divided into two groups. In the hypoxia-LPS group (n=15), probands were exposed to hypoxia (FiO2 10.5%, simulated attitude 4500 m) for 4h followed by a single LPS injection (0.4 ng/kg). In the LPS control group (n=15), only LPS was administered. Physiological parameters were measured and blood samples were drawn at different time points (baseline up to 24h). Immune cells were quantified by flow cytometry. Cytokines were detected in plasma via ELISA.

Results: Oxygen saturation was significantly reduced upon hypoxia exposition and restored to baseline after hypoxia withdrawal. Hypoxic conditions resulted in decreased blood pressure, CD4+ lymphocytes and CD14+ monocytes, while systemic IL-6 concentration was elevated compared to baseline. Hypoxia priming enhanced the LPS induced increase in body temperature and IL-6 and TNF-α plasma levels compared to LPS controls.

Conclusions: In summary, hypoxia priming aggravates the inflammatory response mediated by LPS characterized by enhanced body temperature and plasma concentrations of pro-inflammatory cytokines in healthy probands. These findings indicate that prior hypoxic conditions promote immune cell activation during inflammatory challenges.

OP22 The sympathetic nervous system - fat/muscle connection: an adaptive hypertensive program

Rainer H. Straub[1], Dario Boschiero[2]

[1]University Hospital Regensburg, Germany; [2]BioTekna Biomedical Technologies, 30020 Marcon, Italy

Obesity and hypertension are positively correlated but overall significance of this connection is not clear. From the standpoint of evolutionary medicine and energy regulation, elevated fat stores but also skeletal muscles have a beneficial role. During starvation or energy expenditure by strong psychomotor (brain) or immune system activities, energy reserves in fat tissue and skeletal muscles are important. They represent a memory of stored energy signalled to the brain and immune system. In addition, high sympathetic nervous system (SNS) activity is necessary to fight, to fly, to forage, and to overcome cold, heat, haemorrhage and other threats. Both, stored energy and the SNS serve the body during energy-consuming events. This article demonstrates a physiological platform that links stored energy in fat tissue and skeletal muscles with SNS activity (blood pressure). It relates the afferent muscle reflex (with muscle secretome) and the afferent adipose tissue reflex (with adipocyte secretome) to SNS activity. A fat/muscle index (FMI) is the ratio of fat mass divided by skeletal muscle mass. FMI determines the proportion of variance of systolic and diastolic blood pressure (SNS activity) with 88% (95% confidence interval: 74-81%). A FMI of 1.0 reflects a balance between fat mass and skeletal muscle mass, which defines an upper normal limit of systolic/diastolic blood pressure of 125/80 mmHg. This platform helps to comprehend the relation between energy stores and SNS activity as an adaptive physiological mechanism, long-term application of which in obesity with low muscle mass leads to hypertension and respective sequelae.

OP23 Melatonin synergizes with vemurafenib/cobimetinib-affected bioenergetic and proto-oncogenic pathways in human melanoma

Jack Möller[1], Christian Becker[1], Verena Raker[1], Rita Dreier[2], Meri K Tulic[3], Agnieszka Wolnicka-Glubisz[4], Andrzej T Slominski[5,6], Kerstin Steinbrnik[1], Markus Böhm[1], Konrad Kleszczynski[1]

[1]Department of Dermatology, University of Münster, Von-Esmarch-Str. 58, 48149 Müster,Germany; [2]Institute of Physiological Chemistry and Pathobiochemistry, University of Münster, Waldeyerstraße 15, 48149 Münster, Germany; [3]Centre Méditerranéen de Médecine Moléculaire (C3M), Université Côte d'Azur, INSERM U1065, 06200 Nice, France; [4]Department of Biophysics and Cancer Biology, Jagiellonian University, Gronostajowa 7, 30-387 Krakow, Poland; [5]Department of Dermatology, Comprehensive Cancer Center, University of Alabama at Birmingham, AL 35294, USA; [6]Pathology and Laboratory Medicine Service, VA Medical Center, Birmingham, AL 35294, USA

Melanoma is a leading cause of cancer deaths worldwide. Although targeted therapy and immunotherapy have improved the outcome of patients with metastatic disease, unwanted side effects are a problem. Melatonin, a well-known endogenous synchronizer of the circadian biorhythm has a variety of promising effects for melanoma biology. It regulates proliferation, apoptosis and oxidative phosphorylation via melatonin-receptors, and receptor-independent pathways due to its lipophilicity. Herein, by using human melanoma cell lines in vitro, we show that melatonin enhances anti-tumor effects of commonly used BRAF/MEK inhibitors, i.e. vemurafenib (VF) and cobimetinib (CB), respectively. Our results demonstrate that compared to VF/CB alone, melatonin significantly reduced proliferation read-outs (colony, drop, scratch or migration assay) and induced of apoptosis (cl. Casp-9, -3, PARP) in melanoma cells. Concurrently, VF/CB+melatonin decreased melanoma invasiveness-related protein (E-cadherin), inducible nitric oxide synthase (iNOS), epithelial cell adhesion molecule (EpCAM), and proliferating cell nuclear antigen (PCNA) which are important players in melanoma tumorgenesis, tumor growth, invasion and metastasis. In addition, we also show that combined treatment with the above inhibitors and melatonin results in significant mechanistic changes in cellular bioenergetic by (i) uncoupling of oxidative phosphorylation (OXPHOS), (ii) attenuation of glycolysis (Seahorse assessment), (iii) dissipation of mitochondrial transmembrane potential (mtΔΨ) (FACS), and (iv) changes in mitochondrial morphology (TEM). These findings extend previously published data and provide new perspectives for the introduction of melatonin as an add-on therapy in future treatment of melanoma-affected patients.

OP24 The memory of the fatty acid system and its role for the immune system and the brain

Rainer H. Straub

University Hospital Regensburg, Germany

Mental memory system has sensory memory, short-term memory, working memory, and long-term memory. Working memory “keeps things in mind in parallel” when performing complex tasks. Similar aspects are already known for immunological memory. However, there exists another one, the memory of the fatty acid system.

This article shows the sensory memory of the fatty acid system, which is the perception apparatus of jejunal enterocytes (CD36, SR-B1, FATP4, FABP1, FABP2) and hepatocytes. In the same cells, the fatty acid short-term memory is located, consisting of a cytoplasmic lipid droplet cycle. Similar like a working memory in the brain, the short-term memory of enterocytes and hepatocytes use parallel processing and recourse to long-term fatty acid memory. The fatty acid long-term memory is far away from these primary points of uptake. It is located in the adipocyte and in cellular membranes.

The process of building a fatty acid memory can be described with constructs like sensing environmental material, encoding, consolidation, long-term storage, retrieval with destabilization, re-encoding, re-consolidation, and renewed long-term storage.

The article illustrates the dynamics of building a fatty acid memory, the information content of environmental fatty acids including the code, the diverse roles of fatty acids in the body, and a new understanding of the expression “you are what you eat”. The memory of the fatty acid system, of the brain, and of the immune system play a decisive role in integrating environmental signals over time (diet and microbiome). Understanding the interactive code will shed new light on health and disease.

OP25 Neuroimmune responses to intranasal poly(I:C) are primed by time of day

Gregory Pearson, Brennan Falcy, Jiexin Wang, Gottwals Stephanie, Santos Nathan, Denaroso Giancarlo, Saïd Akli, Ilia Karatsoreos

University of Massachusetts Amherst, United States of America

BACKGROUND. Time of day impacts survival following exposure to a neurotropic virus. Our preliminary work demonstrates that the olfactory bulb (OB), a site of neurotropic virus entry into the brain, shows rhythmic expression of >20% of its neuroinflammation-related transcriptional profile. Here, we investigate how time of day impacts OB neuroimmune responses. We hypothesized that time of day primes the OB to mount differential neuroimmune responses to an intranasal poly(I:C) challenge.

METHODS. First, we intranasally challenged male mice at the start of the resting phase (ZT0) or the start of the active phase (ZT12) with poly(I:C) and collected tissues at 3-, 12-, and 24-hours post-inoculation. OB transcriptional responses were measured using NanoString technology. Second, we intranasally challenged male mice with vehicle or poly(I:C) at ZT0 or ZT12. We then isolated OB microglia at 24 hours post-inoculation and used imaging flow cytometry to analyze microglia.

RESULTS. First, we determined that time of day alters the OB's neuroinflammation-related transcriptional response to intranasal poly(I:C). Specifically, we determined that intranasal poly(I:C) induces antiviral and innate immune pathway responses in the olfactory bulb, and that these responses unfolded more rapidly in mice challenged at ZT12 compared to ZT0. Second, we observed a greater change in CD11b surface expression by OB microglia following intranasal poly(I:C) at ZT12 versus ZT0.

CONCLUSION. We conclude that time of day primes the OB to mount differential neuroimmune responses to intranasal inflammatory stimuli. This priming may provide a gating mechanism underlying differential susceptibility to neurotropic virus exposure via the nasal route.

OP26 Does the chronic beta2 adrenergic receptor stimulation of asthma patients alter systemic NK cell function?

Martin Obholzer[1], Maren Claus[1], Sabine Wingert[1], Elisabeth Hennes[2], Michaela Schedel[3], Ina Haasler[3], Silvia Capellino[1], Carsten Watzl[1]

[1]Leibniz Research Centre for Working Environment and Human Factors Dortmund, Germany; [2]Max Planck Institute of Molecular Physiology Dortmund, Germany; [3]Ruhrlandklinik - University hospital Essen, Germany

Background & Aim:

Epinephrine interacts with natural killer (NK) cells via the beta2 adrenergic receptor (beta2AR). Our previous results show that acute epinephrine stimulation leads to transient inhibition of NK cells while chronic epinephrine exposure desensitizes the beta2AR in vitro. We therefore aimed to find out if NK cells of asthma patients, who use long-acting beta2AR agonist as daily therapeutics, show desensitized beta2AR function similar to chronically treated NK cells in vitro.

Material & Methods:

PBMCs from healthy donors (n=10) and asthma patients (n=10) were functionally analyzed for degranulation by CD107a expression, LFA-1 Ligand complex-based adhesion assay (LCAA) and IFNg ELISA. In comparison, NK cells from healthy subjects (n≥5) were chronically or acutely stimulated with beta2AR agonist and functionally analyzed. Additionally, NK cell killing and cytoplasmatic cAMP concentration were determined by IncuCyte® S3 and cAMP ELISA.

Results & Discussion:

In vitro, acute epinephrine exposure of NK cells induces 8-fold increased cAMP levels, which results in a decreased adhesion capacity, IFNg production, degranulation, and reduces the killing capacity by 20%. In contrast, chronic epinephrine stimulation decreases cytoplasmatic cAMP levels and completely abolishes the inhibitory effects of acute epinephrine stimulation. Interestingly, NK cells of asthma patients, with a chronic beta2AR agonist treatment, showed similar effects to healthy subjects on degranulation, LFA-1 activity or IFNg production under acute epinephrine stimulation. Therefore, PBMCs from asthma patients treated with beta2AR agonist can still react to epinephrine exposure as local treatment does not affect systemic NK cells.

OP27 **MASP-3, and not MASP-1, is the main lectin pathway associated complement protease in mouse brain: evidence for a MASP-3/C3 complosome in astrocytes**

Martin K.H. Schäfer[1,2], Anna-Lena Schlegelmilch[1,2,3], Mirjam Bertoune[1,2], Nathalie Große[1,2], Christian Wächter[4], Ralf Kinscherf[1], Eberhard Weihe[1,2]

[1]Department of Medical Cell Biology, Institute of Anatomy and Cell Biology, University of Marburg, Germany; [2]Center for Mind, Brain and Behavior, University of Marburg, Germany; [3]Department of Neurology, University Medical Center, Johannes Gutenberg University, Mainz Germany; [4]Department of Cardiology, University Hospitals Marburg, Marburg, Germany

Mannose-associated serine proteases (MASPs) play a central role in activating the lectin pathway of the complement system during neurodevelopment and in the adult brain. They derive from two genes, with the alternatively spliced MASP1 gene producing MASP-1, MASP-3, and the inhibitor MAp44. MASP1 gene polymorphisms can lead to severe diseases including sepsis, blood clotting, impaired brain development and neurological diseases. In brain, MASP-1 is regarded as the main MASP1 gene product in spite of lacking confirmatory transcriptional data. Thus, we performed detailed splice variant analyses in C57BL/6 mouse brain at the cellular level in vitro and in vivo.

MASP1 splice variants and complement expression in brain tissue extracts and primary glial cultures were measured by RT-qPCR. Cellular expression patterns and phenotype identification in developing and adult mouse brain was performed with in situ hybridization assays.

Using primers and probes specific for the MASP-1 heavy chain, common to all Masp1 gene transcripts, we could demonstrate that the Masp1 gene is expressed in all brain regions. However, splice variant-specific RT-qPCR and ISH show that MASP-3 and MAp44 coding splice variants are the abundant RNA transcripts in mouse brain, while MASP-1 coding transcripts are below the detection threshold. The analysis of astrocyte and microglial RNA extracts revealed that MASP-3, coexpressed with C3, is the major isoform in astrocytes.

Contrary to the current view, our data suggest that MASP-3, and not MASP-1, is the main protease for local complement activation in the healthy and injured brain with a key function in the astrocytic C3/complosome.

OP28 Sex-specific effects of dopaminergic stimulation on peripheral immune cell response

Leonie Fleige, Silvia Capellino

IfADo- Leibniz Research Centre for Working Environment and Human Factors, Germany

Background: It has already been described that sex-specific differences in dopamine signalling occur in a neurological context regarding dopamine release or dopamine receptor expression. However, little is known about the influence of dopamine on peripheral immune system considering sex. A gain of knowledge in this field could be applied to treatment of infections or defects of the immune system like autoimmune diseases.

Methods: Blood was taken from healthy men and women and PBMCs were isolated. In vitro stimulations were performed using a D1- or D2-like agonist together with CpG ODN2006. Activation marker expression was analysed after 24h of stimulation via flow cytometry and cytokine secretion via Legendplex.

Results: Dopaminergic stimulation increases the expression of the early activation marker CD71 on B cells from women and men. Meanwhile, the change in CD86 or HLA-DR expression on B cells or monocytes points towards an immune cell activation for women while no change or even a downregulation of these activation markers is observable for men. These findings are consistent with cytokine secretion: MCP1, IL-6 and IL-18 are upregulated via dopaminergic stimulation in women and downregulated in men.

Conclusion: Stimulations with D1- and D2-like agonists show similar effects indicating that no clear distinction between D1- and D2-like pathway can be made as already described for the neuronal system. Dopaminergic stimulation leads to proinflammatory responses of PBMCs in women and to antiinflammatory effects in men. This underlines that a distinction between sexes is necessary, also in the context of neuro-immune interaction.

OP29 TBI is associated with fast DC maturation and splenic immune modulation

Jin Zhang[1], Sruthi krishnamurthy[1], Fanjian Li[1], Markus Huber-Lang[2], Francesco Roselli[1,3], Florian olde Heuvel[1]

[1]Dept of Neurology, Ulm University, Germany; [2]Institute of Clinical and Experimental Trauma-Immunology, Universityclinic Ulm, Germany; [3]DZNE Ulm, Ulm, Germany

Systemic inflammatory responses have been reported after traumatic brain injury (TBI), with almost all organs affected. The spleen, one of the most important immune regulatory organs, shows high interaction with the brain, known as the brain-spleen axis. Both brain-derived mediators as well as nerve fibres have been reported to directly affect immune cells in the spleen. We have previously investigated the effects of TBI on splenic immune cells, showing a fast maturation of splenic dendritic cells 3h after an experimental TBI. However, how the inflammatory cytokine response changes to TBI, and possibly DC maturation, remains largely unknown.

We have performed transcriptional analysis, fluorescent staining and in situ hybridisation of spleen sections to investigate cellular mechanisms in immune cells 3h post experimental TBI. In addition, we have performed large scale cytokine, angiogenesis, and phospho-signaling arrays to determine functional immune responses in spleen samples post TBI.

We found a significant FLT3/FLT3L upregulation 3h post TBI, resulting in an enhanced phosphorylation of FLT3 in CD11c+ dendritic cells, which increased the protein synthesis and maturation process of dendritic cells, followed by an increased immunity. Furthermore, we found a large-scale cytokine modulation, vascular involvement, and phosphorylation of signaling events 3h post TBI.

These findings indicates that there is a fast maturation and immunity of splenic dendritic cells upon TBI associated with FLT3/FLT3L signaling. Additionally, this data points out that TBI is regulating splenic immune, vascular and signaling responses. Showing the involvement of TBI on spleen functioning and its effect on systemic inflammatory responses.

OP30 Sleep promotes T-cell migration towards CCL19 via growth hormone and prolactin signaling in humans

Estefania Martinez-Albert[1,2], Nicolas D. Lutz[1,2], Robert Hübener[2], Stoyan Dimitrov[2], Tanja Lange[3,4], Jan Born[2,5], Luciana Besedovsky[1]

[1]Institute of Medical Psychology, Ludwig-Maximilians-Universität München, Munich, Germany; [2]Institute of Medical Psychology and Behavioral Neurobiology, Eberhard Karls University of Tübingen, Tübingen, Germany; [3]Department of Rheumatology and Clinical Immunology, University of Lübeck, Lübeck, Germany; [4]Center of Brain, Behavior and Metabolism (CBBM), University of Lübeck, Lübeck, Germany; [5]Werner Reichardt Centre for Integrative Neuroscience, Eberhard Karls University of Tübingen, Tübingen, Germany

Background: Sleep boosts the formation of adaptive immunity, e.g., after vaccination. A promoting effect of sleep on T-cell migration to lymph nodes, where adaptive immune responses are initiated, has been proposed as underlying mechanism. However, direct evidence for this hypothesis is lacking.

Methods: 14 healthy participants were examined in the sleep laboratory during a normal sleep-wake cycle and during 24 hours of continuous wakefulness. Blood was collected every 4 hours to determine T-cell migration using Transwell® chemotaxis assays with or without the lymph-node homing chemokine CCL19 or the inflammatory chemokine CCL5. In additional ex vivo and in vitro experiments, the effects of plasma collected from sleeping vs. awake participants and of the sleep-dependent hormones growth hormone (GH) and prolactin on T-cell migration were investigated.

Results: Sleep selectively increased the spontaneous as well as CCL19-directed migration of total CD3, CD4, CD8 T-cells, and naïve subsets, without affecting migration towards CCL5. Furthermore, incubation of T-cells from healthy donors with plasma collected from participants of the in vivo experiment during sleep enhanced CCL19-directed T-cell migration compared to plasma collected during wakefulness. This effect was blunted following blockade of GH and prolactin signaling. This finding is in line with additional in vitro experiments demonstrating increases in T-cell migration towards CCL19 following incubation of the cells with GH and prolactin.

Conclusion: Sleep selectively promotes T-cell migration towards CCL19 by enhancing GH and prolactin signaling. These findings reveal a potential underlying mechanism of the boosting effect of sleep on adaptive immunity.

Poster presentations

PP01 Treatment context fails to elicit conditioned sickness responses in rats

Lisa Trautmann, Kirsten Dombrowski, Sebastian Wenzlaff, Laura Lückemann, Manfred Schedlowski, Harald Engler

Institute of Medical Psychology and Behavioral Immunobiology, Center for Translational and Behavioral Neurosciences (C-TNBS), University Hospital Essen, University of Duisburg-Essen, Essen, Germany

Background: Sickness symptoms are common side effects of immuno- and chemotherapy. During the course of such therapies, which typically involve repeated treatment cycles, many patients develop sickness symptoms after sole re-exposure to the treatment context. The mechanisms underlying this anticipatory nocebo response remain largely unknown and can only be partially addressed in patients, calling for translational animal studies.

Methods: This study aimed to establish a contextual learning paradigm in rats as a translational animal model of conditioned sickness. During learning phase, animals received an intraperitoneal injection of endotoxin (lipopolysaccharide, LPS) as sickness-inducing stimulus and were subsequently placed into a novel context consisting of visual, tactile, and olfactory cues. This protocol was repeated for up to three times with increasing doses of LPS to vary the amount of prior learning experience. During recall phase, animals were re-exposed to the treatment context alone to test for conditioned behavioral and physiological sickness responses.

Results: During initial learning, LPS-treated animals mounted strong behavioral and physiological sickness responses including immune activation and decreased explorative behavior. However, independently of the number of association trials, re-exposure to the initial treatment context failed to elicit conditioned sickness responses both at the physiological and behavioral levels during recall test.

Conclusions: Difficulties in obtaining a successful association between treatment context and sickness symptoms might be due to the complexity of the context used or a lack of contingency awareness.

PP02 Alleviating Allergic Skin Responses – A Prospective Conditioning and Open Label Placebo Study

Stefanie Hölsken[1], Eva Holubek[2], Frederik Krefting[2], Senta Mühlhaus[1], Joachim Dissemond[2], Manfred Schedlowski[1,3], Wiebke Sondermann[2]

[1]Institute for Medical Psychology and Behavioral Immunobiology, University Hospital Essen, Germany; [2]Department of Dermatology, Venereology and Allergology, University Hospital Essen, Germany; [3]Department of Clinical Neuroscience, Osher Center for Integrative Medicine, Karolinska Institutet, Stockholm, Sweden

Background: Allergic reactions provide a promising model to analyze mechanisms steering placebo effects, since high placebo rates in clinical studies suggest susceptibility to psychological mechanisms. Placebo effects are mainly mediated via associative learning procedures and patients' treatment expectations. Experimental approaches have initially studied placebo effects in allergic patients by employing classical conditioning paradigms to affect symptoms. However, the role of treatment expectation is still largely unclear. Thus, our study aimed to establish a model applicable in healthy volunteers to disseminate the role of prior learning experiences as well as treatment expectation.

Methods: Altogether, 101 healthy volunteers were randomized into three groups. One group underwent a classical conditioning regimen: in the acquisition week, an anti-histaminergic drug (unconditioned stimulus/US) was paired with a novel gustatory (conditioned) stimulus (CS); during retrieval, participants were re-exposed to the novel stimulus alone. The second group provided a context-control condition, undergoing acquisition as group one, but were not re-exposed to the CS during retrieval. The third group received placebo pills, which were administered together with information about the beneficial effects found in previous "open label placebo" studies. At five time-points, skin symptoms were provoked using a histamine prick test. The objective parameters erythema and wheal size as well as perceived itch were analyzed.

Results: Data analysis is still ongoing and final results will be presented at the conference.

Conclusion: Our results may help elucidate the mechanisms underlying placebo responses in allergic reactions and the question of generalizability of findings from patient studies in the field of allergy.

PP03 The impact of chronic inflammation on fear extinction in a preclinical mouse model of IBD

Lena Nonnweiler[1], Sebastian Wenzlaff[1], Sigrid Elsenbruch[2], Harald Engler[1]

[1]Institute of Medical Psychology and Behavioral Immunobiology, Center for Translational and Behavioral Neurosciences (C-TNBS), University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [2]Department of Medical Psychology and Medical Sociology, Ruhr University Bochum, Bochum, Germany

Background: Our earlier findings in healthy humans under acute experimental inflammation and in patients with chronic inflammatory bowel disease (IBD) suggest that multiple hits of inflammation may result in structural/functional alterations in the fear extinction network, facilitating maladaptive fear learning and memory processes. The aim of this ongoing study is to investigate the influence of recurrent or chronic inflammation on the extinction of conditioned fear and its neurobiological underpinnings in a preclinical animal model of IBD.

Methods: The dextran sulfate sodium (DSS) mouse model of colitis is combined with an auditory fear conditioning paradigm. For the induction of acute colitis, mice receive 4% DSS via drinking water for seven consecutive days, followed by a two-week recovery period. Chronic colitis is induced by repeated cycles of DSS treatment. Water-treated mice serve as controls. After one, two, or three treatment cycles, mice undergo an auditory fear learning and extinction task during either acute disease or remission. Functional and neuroinflammatory changes in the key regions of the fear extinction network are assessed by measuring neuronal and microglia activation as well as cytokine and BDNF expression after fear acquisition, extinction training, or recall.

Results: Gene expression analysis revealed initial evidence for an altered pro-inflammatory cytokine and neurotrophin expression in the hippocampus of mice with chronic colitis compared to healthy controls. Behavioral and brain immunohistochemical analyses are currently underway.

Conclusions: Our preliminary data support the hypothesis that chronic IBD leads to molecular changes in brain regions relevant for fear extinction.

PP04 The association between telomere length and the expression of DNA repair genes in the context of traumatic stress

Hannah Keppler[1], Alexander Behnke[1], R. Nehir Mavioglu[1], Melissa Hitzler[1], Iris-Tatjana Kolassa[1], María Moreno-Villanueva[2,3], Matthias Mack[1]

[1]Clinical and Biological Psychology, Institute of Psychology and Education, Ulm University; [2]Molecular Toxicology, Department of Biology, University of Konstanz; [3]Department of Sport Science, Human Performance Research Centre, University of Konstanz

Introduction: Traumatic stress can jeopardize somatic and mental health. Biologically, traumatic experiences can be manifested in elevated levels of oxidative stress and consequently in an impaired DNA integrity. We investigated the association of telomere length as a proxy for cellular stress and the expression of DNA damage repair genes poly (ADP-ribose) polymerase 1 (PARP1) and X-ray repair cross complementing 1 (XRCC1) in the context of traumatic stress.

Methods: In a cohort of postpartum women with and without experiences of childhood maltreatment (CM, N=100), telomere length was assessed via monochrome multiplex quantitative polymerase-chain reaction (PCR) and gene expression was assessed via quantitative PCR in immune cells. In addition, in a cohort of refugees exposed to war, torture, and civil traumatic events (N=24), telomere length was assessed via southern blot analysis and gene expression was assessed via semi-quantitative PCR in immune cells.

Results: In postpartum women with experiences of CM, telomere length and PARP1 expression were negatively associated (pHolm=.003, ηp^2=0.1). This effect was not present in women without experiences of CM (pHolm=.635, ηp^2=0.003). In refugees exposed to war and torture, telomere length was negatively associated with both PARP1 (p=.02, ηp^2=0.23) and XRCC1 (p=.011, ηp^2=0.27) expression.

Conclusion: Traumatic stress involves upregulated DNA damage repair, which is negatively linked to telomere length, in immune cells. Our results endorse the assumption that traumatic stress can lead to an allostatic load, likely mediated by oxidative stress, in response to which the body needs to upregulate compensatory mechanisms which are energy consuming by nature.

PP05 Immunization with Mycobacterium vaccae prevents negative effects of prenatal stress

Jessica Schiele[1], Pei-Ling Tsai[2], Dominik Langgartner[1], David A. Slattery[2,3], Stefan O. Reber[1,3]

[1]University Clinic Ulm, Germany; [2]Translational Psychiatry, Department of Psychiatry, Psychosomatics and Psychotherapy, Frankfurt, Germany; [3]these authors contributed equally

The postpartum period represents a time with high risk for women to develop mood and anxiety disorders, such as postpartum anxiety (PPA) and postpartum depression (PPD). PPA and PPD, often comorbid, lead to impaired maternal-infant attachment during the critical stages of early brain development and increase the risk of the offspring developing long-term behavioural and emotional problems, including increased vulnerability to mental illness. The aim of this study is to determine whether a heat-killed preparation of Mycobacterium vaccae (M. vaccae) given repeatedly prior to mating via the intragastric (i.g.) route can protect the offspring from the negative behavioral and physiological effects of prenatal stress. Therefore, adult nulliparous C57BL/6N female mice will be i.g. administered with M. vaccae (once per week over three weeks) prior to mating, followed by 13 consecutive days of pregnancy stress. In detail, pregnant mice of the stress groups will be exposed alternatively to daily restraint (2 x 1h) and overcrowding/social instability. Around PND 49, experimental male and female offspring will be assessed for general and social anxiety employing the Open Field/ Novel Object, Elevated Plus-Maze, and Social Preference/ Avoidance Tests, as well as for depressive symptoms using the Forced Swim Test and Saccharin Preference Test, before their corticosterone response to acute restraint stress will be assessed. Generated data will be presented and discussed at the GEBIN Conference in September.

PP06 SARS-CoV-2 specific sIgA in saliva increases after disease-related video stimulation

Judith Keller[1], Alex Dulovic[2], Jens Gruber[2], Johanna Griesbaum[2], Nicole Schneiderhan-Marra[2], Clemens Wülfing[3], Jana Kruse[1], Annika Hartmann[1], Esther Diekhof[1]

[1]Universität Hamburg, Germany; [2]NMI Natural and Medical Sciences Institute, Reutlingen, Germany; [3]Interdisciplinary Neurobiology and Immunology, Hamburg, Germany

Introduction

Secretory immunoglobulin A (sIgA) in saliva is the most important immunoglobulin fighting pathogens in the respiratory tract and may thus play a role in preventing SARS-CoV-2 infections. Previous studies showed that visual perception of disease cues causes an increase in total sIgA in saliva, which suggests a proactive immune response that may also correlate with associated aversive feelings. To gain a better understanding of the plasticity of SARS-CoV-2-specific mucosal antibodies, we investigated this proactive change to visual disease cues in spike- as well as RBD-specific sIgA.

Method

Using a within-subject design, we showed 45 participants either a disease video displaying people with respiratory symptoms resembling realistic situations of increased airborne contagion risk, or a control video of healthy people. Furthermore, we recorded self-reported trait and state feelings of perceived disgust, contagion risk and interoception.

Result

The disease video triggered an increase in spike-specific sIgA, which was absent after the control video. This increase further correlated inversely with revulsion and aversive feelings elicited by the disease video. In contrast, the receptor-binding domain-specific sIgA did not increase after disease stimulation.

Conclusion

The results indicate differential roles of the two salivary antibodies in response to visual predictors of airborne contagion. The observed plasticity of spike-specific salivary antibody release after visual simulation of enhanced contagion risk suggests a role in immune exclusion. Furthermore, the inverse correlation of spike-specific sIgA with self-reported feelings are in line with the hypothesis of a compensatory relationship between behavioral and physiological responses to situations with increased contagion potential.

PP07 Comparison of cytokine levels and PBMC subsets in male and female axial Spondyloarthritis patients

Mia Juditzki[1], Dimitra Karagkiozidou[2], Styliani Tsiami[2], Christian Schütz[2], Xenofon Baraliakos[2], Silvia Capellino[1]

[1]IfADo - Leibniz Research Centre for Working Environment and Human Factors, Department of Immunology, Dortmund, Germany; [2]Rheumazentrum Ruhrgebiet, Ruhr University Bochum, Herne, Germany

Background: Female and male axial Spondyloarthritis (axSpA) patients showed different disease progression, treatment efficacy, and different amounts of inflammatory biomarkers, suggesting that there are sex-specific differences in the pathophysiology of axSpA. However, little is known about sex-specific differences in axSpA pathology. This study aims to find sex-specific differences in axSpA-related biomarkers and peripheral blood mononuclear cell (PBMC) subsets in biologically naïve nr-axSpA and r-axSpA patients.

Methods: The study includes biologically naïve nr-axSpA (males n=9, females n=6) and r-axSpA patients (males n=26, females n=10), with high disease activity, and age-matched back pain controls (males n=7, females n=14). Levels of HGF, IL-6, IL-10, IL-12(p40), TNF-alpha, VEGF, IL-17A, IL-22, IL-23, MMP-3, Osteocalcin, and Osteopontin were analyzed in plasma by multiplex analysis. Flow cytometry was used to differentiate PBMC subsets.

Results: As previously shown, we observed higher levels of IL-6 in r-axSpA females than in males whereas male nr-axSpA patients revealed significantly higher plasma IL-6 levels than females ($p<0,05$). Similar results were observed for HGF. In addition, male r-axSpA patients had higher MMP-3 concentrations than females ($p<0,05$). So far, flow cytometry data did not indicate any significant differences in PBMC subsets between males and females with nr- or r-axSpA.

Conclusion: Plasma expression of some cytokines such as IL-6, HGF, and MMP-3 is sex- and disease-subgroup-specific, which demonstrates the importance and clinical relevance of sex- and disease-subgroup-specific analysis. Such comprehensive studies will help to understand the pathophysiology of axSpA and to identify sex- and disease-subgroup-specific therapeutic targets to improve personalized treatment response.

PP08 Conditioned Placebo Effects in Allergic Contact Dermatitis

Yasmin Salem[1], Martin Hadamitzky[1], Stephan Leisengang[1], Laura Heiss-Lückemann[1], Marie Jakobs[1], Manfred Schedlowski[1,2]

[1]University Hospital Essen, Germany; [2]Karolinska Institutet, Sweden

Background: Allergic Contact Dermatitis is an inflammatory skin disease which requires the use of immunosuppressive medication. The amount of adverse side effects induced by the respective therapeutic drugs urges the need for developing alternative or supportive treatment strategies. Recent knowledge documents that associative learning protocols may be used for drug dose reduction while simultaneously maintaining treatment efficacy.

Methods: An established paradigm of taste-immune conditioning is applied in a disease model of allergic contact hypersensitivity (induced by DNFB) in rats, where a novel taste (saccharin; conditioned stimulus/CS) is paired with an injection of the immunosuppressive drug cyclosporine A (CsA) as unconditioned stimulus (US). After three CS/US pairings (acquisition), animals are sensitized with DNFB. Later, retrieval starts by presenting the CS, while clinical symptoms are triggered by DNFB exposure.

Results: Animals with contact hypersensitivity induced by DNFB are used to verify treatment improvement by conditioning. Preliminary experiments determined the therapeutic dose and the study design. In this paradigm, taste-immune associative learning is expected to reduce symptoms and inflammation in conditioned animals.

Conclusions: Reframing continuous drug intake as a learning process may open a new path for treatment improvement in diseases such as allergic contact dermatitis to reduce drug dosages, unwanted detrimental drug side effects, as well as treatment costs.

PP09 Endocannabinoid Hair Concentrations in Women with Childhood Maltreatment and their Children from late Pregnancy to One Year after Birth

Melissa Hitzler[1], Lynn Matits[1,2], Anja Gumpp[1], Alexandra Bach[1], Ute Ziegenhain[3], Wei Gao[4], Alexander Behnke[1], Iris-Tatjana Kolassa[1]

[1]Clinical and Biological Psychology, Institute of Psychology and Education, Ulm University, Germany; [2]Division of Sports and Rehabilitation Medicine, Department of Medicine, Ulm University Hospital, Ulm, Germany; [3]Department of Child and Adolescent Psychiatry, Ulm University Hospital, Ulm, Germany; [4]Department of Biopsychology, Technische Universität Dresden, Dresden, Germany

Background. While the negative effects of CM have been extensively studied, less focus has been placed on whether CM-effects are passed on a biological level to the next generation. Thereby, CM might affect the endocannabinoid (eCB)-system which critically modulates inflammation and the endocrine stress-response. Thus, we investigated the eCB-system of women with and without CM and their infants using hair samples representing eCB level accumulated during the last trimester of pregnancy and 10–12 months postpartum. Method. CM was assessed with the Childhood Trauma Questionnaire. 3cm-hair-strands were collected from mothers and children (N = 170 resp. 150) to measure anandamide (AEA), 2/1-arachidonoylglycerol (2-AG/1-AG), stearoylethanolamide (SEA), oleoylethanolamide (OEA), and palmitoylethanolamide (PEA). Results. Maternal 2-AG/1-AG levels increased and SEA levels decreased from late pregnancy to one year postpartum. Maternal CM was associated with lower SEA levels in late pregnancy, but not at one year later. In the children's hair, 2-AG/1-AG levels increased and SEA, OEA, and PEA levels decreased over time. Maternal CM was associated with higher OEA levels in infants in late pregnancy, but not one year later. Conclusion. We provide first longitudinal evidence for changes in the eCB-system activity in mothers and infants from pregnancy to one year later. Maternal CM influenced eCB in mothers and their unborn. As this association was limited to pregnancy, maternal CM seems not to persistently alter the offspring's eCB-system regulation. Future research needs to investigate the importance of alterations in the eCB-system for immunoregulation, pregnancy and health as well as developmental trajectories of children.

PP10 Proactive mucosal immune responses in virtual reality depend on the sense of presence

Esther K. Diekhof, Agon Kusari, Frank Steinicke, Judith K. Keller

Universität Hamburg, Germany

The capacity to recognize infected conspecifics and to react accordingly to reduce contagion risk is crucial for survival. Evidence suggests that the mere visual perception of disease cues can proactively enhance mucosal immune responses even without actual pathogen exposure. Previous studies used videos and photos of sick persons to stimulate the immune system. Whether a proactive release of secretory immunoglobin A (sIgA) can also be evoked in the immersive setting of a virtual environment (VE) remains elusive. Here, we simulated a scenario of enhanced airborne contagion risk and assessed associated changes in salivary sIgA.

We created a virtual bus stop with ten interactive agents. Participants performed the "Make-All-Agents-Smile-Task", which required close approach of and eye-contact with each agent until he/she smiled. In the contagion scenario, some agents also sneezed, either directly before smiling or at predefined time intervals. The control scenario had an identical setting, yet nobody sneezed. We tested 70 healthy participants in a between-subjects design to restrict potential effects of cybersickness on sIgA. We also assessed sense of presence in the VE, and perceived disgust and contagion risk.

We found that sIgA was unrelated to cybersickness. However, sIgA increased in both scenarios, and the increase also correlated with the perceived involvement in the VE. This suggests that the intimate social interactions with virtual agents were sufficient to increase sIgA, and particularly so if a heightened sense of presence was experienced in the VE. Overall, virtual reality may thus represent a promising tool to provoke proactive immune responses.

PP11 Influence of LPS and hypoxia on the dopaminergic pathway in the peripheral immune system

Gina Wagener[1], Leonie Fleige[1], Marie Jakobs[2], Tina Hörbelt-Grünheidt[2], Silvia Capellino[1]

[1]Leibniz Research Centre for Working Environment and Human Factors, Department of Immunology, Germany; [2]Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, Germany

Background: Besides its effects as neurotransmitter in the central nervous system (CNS), dopamine also affects the immune system. It is known that LPS and hypoxia influence the neuronal dopaminergic pathway. However, little is known about the effect of these stimuli on the dopaminergic pathway in human immune cells, thus underlining the importance of this study.

Methods: 29 healthy men were recruited (21-33 years). In LPS-Hypoxia group (n=9), LPS was injected (0.4 ng/ml), following by 4h in hypoxia chamber. In Hypoxia-LPS group (n=14), after 4h in hypoxia chamber LPS was injected. In LPS group (n=6), only LPS was injected. Blood samples were collected at ten different time points (0h-24h). Expression of dopamine receptors (DRs) on PBMC subpopulations was quantified via flow cytometry and dopamine in serum via ELISA. The study was approved by the ethical committee and all subjects gave written consent.

Results: Dopamine release in serum was modulated 1h after LPS injection, while upregulated D1 and D3DR expression on NK cells and monocytes, and downregulated D2 and D4DR expression in NK cells, B cells and T cells was observed after 24h. Hypoxia did not affect DR expression.

Conclusions and Outlook: Changes in DR and dopamine levels suggest that LPS regulates the dopaminergic pathway also outside of the CNS. Unfortunately, only male subjects were included in this study. Since our latest findings show sex-specific differences in the dopaminergic pathway in immune cells, differences between men and women via LPS stimulation will be further investigated in PBMCs in vivo and in vitro.

PP12 Mycobacterium vaccae immunization-- Inducing resilience to stress during pregnancy in the dam

Pei-Ling Tsai[1], Jessica Schiele[2], Dominik Langgartner[2], Stefan O. Reber[2,3], David A. Slattery[1,3]

[1]Laboratory of Translational Psychiatry, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Goethe University, 60528 Frankfurt/Main, Germany; [2]Laboratory for Molecular Psychosomatics, Department of Psychosomatic Medicine and Psychotherapy, Ulm University Medical Center, 89081 Ulm, Germany; [3]these authors contributed equally

Postpartum mood disorders like postpartum depression (PPD) and anxiety (PPA) affect 5-13% of mothers and are often comorbid. The high prevalence and negative impacts on mothers and infants indicate the necessity for promising treatment/ prevention of postpartum-associated psychiatric disorders. Chronic low-grade inflammation is a potential mechanism that contributes to postpartum mood disorders. Previous studies in adult mice have shown that repeated subcutaneous administrations of Mycobacterium vaccae prior to stressor exposure protect against stress-induced anxiety through its immunoregulatory property. Therefore, we hypothesize that repeated M. vaccae administrations prior to mating can protect the dam from the detrimental effects of pregnancy stress. Female C57BL/6N mice will receive weekly*3 intragastric M. vaccae administrations prior to mating. Pregnancy stress comprises 13 consecutive days with alternating days of restraint stress and overcrowding/ social instability, followed by single housing for delivery. During the first week of postpartum, maternal care and motivation will be assessed by observing the nursing behaviors and performing the pup retrieval test. Furthermore, anxiety- and/or depression-related behaviors will be tested with open field/novel object, social- and saccharin preference tests. Tissues from the dams will also be collected for further HPA axis, peripheral and central inflammatory response analyses. We expect dams that underwent pregnancy stress will manifest signs of chronic stress, indicated by increased anxiety, lack of or exaggerated maternal care to the pups, reduced saccharin preference, as well as altered stress-related physiological parameters. Furthermore, we anticipate that dams administered with M. vaccae show a stress-resilience phenotype with restored stress-related behaviors and physiological alterations.

PP13 Differences of dietary group on blood iron parameters, depressive and somatic symptoms in women and men: NuEva Study

Ellen Armella Bisle[1], Birthe Rackwitz[2], Alexander Behnke[1], Alina Seidel[3], Michael Kiehntopf[4], Kristin Kipp[5], Christine Dawczynski[2], Iris-Tatjana Kolassa[1]

[1]Ulm University, Germany; [2]Friedrich Schiller University Jena, Germany; [3]Bonn University, Germany; [4]University Hospital Jena, Germany; [5]Sophien- and Hufeland Hospital Weimar, Germany

Iron is decisive for the body's oxygen transport and mitochondrial energy production. Besides recycling of body-intern iron, nutrition - especially meat - is the most bioavailable iron source. Persons following a plant-based diet more often show depressive symptoms like fatigue and feelings of loss of energy. Thus, decreased iron intake might be one connecting link between diet and depressive symptom. Additionally, iron deficiencies as well as depressive and somatic symptoms show higher prevalence in women, indicating a potential sex-specific effect. Therefore, this study aims to elucidate effects of diet and sex on blood iron parameters as well as depressive and somatic symptoms. Healthy adults (N=134) following four different diets (western diet, flexitarian, vegetarian, or vegan) were included. All groups received twelve months of nutritional coaching followed by blood collection, depressive and somatic symptoms assessment (PHQ-9/-15) 24 months after inclusion. There were no differences of blood iron parameters, depressive or somatic symptoms between the dietary groups (all p's≥.06). As expected, men consuming a western diet show higher ferritin values, compared to all other diet groups. No sex × diet interactions for other blood iron parameter were found. Sex-specific correlation analyses showed small significantly positive associations of erythrocytes, hematocrit, and hemoglobin with depressive and somatic symptoms. Taken together, increased blood iron parameters were associated with increased depressive and somatic symptoms, supporting the idea of a U-shaped connection between iron status and depressive and somatic symptoms.

PP14 Affected motivated behavior under subjective fatigue in healthy individuals

David S. Stolz, Finn Luebber, Tanja Lange, Stefan Borgwardt, Malte Ziemann, Gabriela Riemekasten, Jan Rupp, Laura Müller-Pinzler, Frederike Wagener, Jan Weis, Frieder M. Paulus, Sören Krach

University of Lübeck, Germany

Background

Fatigue is a prominent symptom in many clinical conditions and is marked by severe mental and physical exhaustion, but its etiology is not yet fully understood. In particular, the underlying motivational processes of fatigue are rarely investigated based on experimental task-based measures.

Methods

In a total of three studies (total N=130), we implement a novel experimental task to assess central processes of motivated behavior, i.e., confidence, effort execution, and their coregulation (study 1; n=48), and tested the reliability of our measures using a test-retest design (study 2; n=27). Finally, we assessed subjective fatigue and motivated behavior in participants once soon after they were vaccinated against SARS-CoV-2, and once without shortly preceding vaccination (study 3; n=55, quasi-experimental, repeated-measures, cross-over design).

Results

We showed that the results from our task aligned with theoretical considerations and that our measures were reliable. Further, we were able to demonstrate that fatigue entails alterations in central processes of motivated behavior. Differences in subjective fatigue between experimental days were associated with reduced confidence, but not with effort execution or their coregulation. In addition, changes in fatigue were associated with diminished goal attainment (i.e., task success), particularly in individuals with higher baseline fatigue, reminiscent of vulnerability-stress dynamics.

Conclusion

Our findings extend previous evidence that key processes of motivated behavior are compromised under fatigue and highlight the importance of vulnerability-stress mechanisms in the etiology of this complex symptomatology.

PP15 An assessment of bacterial induction of mouse neutrophil extracellular traps in vitro using lipopolysaccharide or Group B Streptococcus

Jessica Hernandez[1], Jan Stoll[1], Marita Meurer[2], Lois Harden[3], Maren von Köckritz-Blickwede[2], Christoph Rummel[1]

[1]Institute of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, Justus-Liebig University Giessen; [2]Institute of Biochemistry & Research Center for Emerging Infections and Zoonoses (RIZ), University of Veterinary Medicine Hannover; [3]Brain Function Research Group, School of Physiology, University of the Witwatersrand

Neutrophil extracellular traps (NETs) are formed by activated neutrophil granulocytes (NG) and serve an important role in pathogen clearance. However, previous studies have also found that NET overexpression can contribute to the pathogenesis of certain disease states by inducing pro-inflammatory cytokines and rapid neurotoxicity through the release of proteases associated with de-condensed DNA released from NGs. Sepsis and meningitis due to invasive group B Streptococcal (iGBS) disease during early infancy is an important cause of child morbidity and mortality. We aimed to investigate the inflammatory response of NGs to gram-negative (lipopolysaccharide, LPS) and gram-positive (GBS) bacterial mimetics to induce NETs in vitro. Bone marrow derived NGs were isolated from the femur and tibia of male and female aged mice (19-22 weeks). To induce NETosis NGs were incubated with LPS (1, 10, or 20 ug/ml) or GBS (MOI 100) alone or in combination with chemokine (C-X-C Motif) ligand 1 (CXCL1, 50 ng/ml). After 3h the cells were fixed and analyzed by immunofluorescence microscopy for the NET markers myeloperoxidase and DNA/Histone1-complex. Supernatants were collected and analyzed by bioassays for TNF-alpha and IL-6. Preliminary results indicate that treatment with GBS alone but not LPS may significantly increase NET formation. Treatments performed in combination with CXCL1 did not increase NET formation in either GBS or LPS groups. Levels of TNF-alpha and IL-6 appeared unaffected by treatment with GBS or LPS but further analysis is required. Together, our ongoing experiments suggest a possible role of NETs in the pathogenesis of iGBS disease.

PP16 Exploring the Interplay Between Adverse Childhood Experiences, Allostatic Load Index, and Mental Health: Insights into Biological Mechanisms and Biomarkers from large scale public access data (Whitehall Study)

Marc N. Jarczok[1], Marion Jarczok[2], Joerg Fegert[2], Vera Clemens[2]

[1]Clinic for Psychosomatic Medicine and Psychotherapy, University Medical Center Ulm, Germany; [2]Department for Child and Adolescent Psychiatry/Psychotherapy, University Medical Center Ulm, Germany

Background

Adverse childhood experiences (ACEs) are considered a major risk factor for mental health problems in adulthood. ACEs induce an activation of the stress system, leading to long-term alterations in the autonomous (ANS), metabolic (MS) and inflammatory systems (IS). These alterations are thought to play a central role in the pathogenesis of mental health problems (MH). The Allostatic load index may capture these biological alterations. The main objective is to investigate the interplay between ACEs, ALI and mental health problems.

Methods

Data were gained from Phase 5 of the Whitehall II cohort study. Cross-sectional data from phase 5 (Conducted between 1997 to 1999) included N=5924 participants with valid data on ALI (based on worst quartile of the population from 11 biomarkers) and health outcomes (SF36, GHQ). Bivariate nonparametric Kendall tau beta correlation analysis as well as mixed linear models were conducted.

Results

ACEs were associated significantly with both increased ALI and poorer mental as well as somatic health. Allostatic load significantly mediated the interplay between ACEs and core aspects of mental and physical health particularly somatoform symptoms scores including pain and physical functioning.

Conclusion

Our results will provide important insights into biological mechanisms involved in somatoform and mental health problems following ACEs, paving the way to mechanism-based biomarkers, a crucial step to improve early detection as well as the development of specific interventions for the prevention of mental health disorders.

PP17 Analysis of the VIP/PACAP system in SIM-A9 cells: evidence for PACAP regulating microglial polarization towards an anti-inflammatory phenotype

Anastasia Possylayeva[1,2], Nathalie Große[1,2], Mirjam Bertoune[1,2], Stephan M.G. Schäfer[3], Christian Wächter[4], Eberhard Weihe[1,2], Ralf Kinscherf[1], Martin K.-H. Schäfer[1,2]

[1]Department of Medical Cell Biology, Institute of Anatomy and Cell Biology, University of Marburg, Germany; [2]Center for Mind, Brain and Behavior, University of Marburg, Germany; [3]Institute of Clinical Pharmacology, Goethe University, Frankfurt, Germany; [4]Department of Cardiology, University Hospitals Gießen and Marburg, Marburg, Germany

BACKGROUND: The neuropeptides PACAP and VIP have neuroprotective and anti-inflammatory properties via VPAC1, VPAC2, and PAC1 receptors, which are widely expressed in the brain, including microglia. Mechanistic effects of these neuropeptides on activated microglia have mainly been studied in vitro using BV2 cells. Here, we investigated the VIP/PACAP system in SIM-A9 cells, a spontaneously immortalized cell line, and compared it to primary microglia. The effect of PACAP and VIP on microglial polarization was also studied.

METHODS: SIM-A9 cells and microglia isolated from C57BL/6 mouse brain were stimulated with LPS, anti-inflammatory cytokines, and PACAP or VIP. RT-qPCR assays were established to monitor expression changes of the VIP/PACAP system and of M1/M2 polarization markers after co-stimulation with PACAP or VIP.

RESULTS: In contrast to BV2, SIM-A9 cells exhibited both VPAC1 and VPAC2 transcripts, which decreased after LPS stimulation. While VPAC1 mRNA levels returned to control levels after 48h, VPAC2 mRNA remained significantly decreased. The proinflammatory response to LPS, which lasted at least 48h, was dampened by co-application of PACAP, which also induced an anti-inflammatory (M2) state. Anti-inflammatory stimulation yielded an up to 500fold mRNA increase of the M2 marker Arg1 and a small increase of VPAC1, but not VPAC2. PAC1, PACAP, and VIP transcripts were below detection.

CONCLUSIONS: SIM-A9 cells show features of activated microglia with downregulated VPAC receptor expression after LPS stimulation. Our results suggest that PACAP has the ability to partially mitigate the LPS-induced expression of M1 markers, while also promoting the induction of an anti-inflammatory M2 state.

PP18 Assessing the Effects of a Stress Management Intervention on Biomarkers of Stress among Small and Medium-sized Enterprise (SME) Leaders: A Randomized Controlled Trial

Michael Gast[1], Marc Jarczok[1], Sophie Merle Hofmann[1], Svenja Schlachter[1,2], Mathias Diebig[3], Rebecca Erschens[4], Susan Gritzka[3], Carla Schröpel[4], Elisabeth Balint[5], Urs Nater[7], Peter Angerer[3], Florian Junne[6], Harald Gündel[1]

[1]Department of Psychosomatic Medicine and Psychotherapy Ulm University Medical Center; [2]Section of Public Mental Health, Department of Psychiatry and Psychotherapy II of the University of Ulm at the BKH Günzburg; [3]Institute of Occupational, Social and Environmental Medicine, Heinrich Heine University Düsseldorf; [4]Department of Psychosomatic Medicine and Psychotherapy, University Hospital Tübingen; [5]Center for mental health, Privatklinik Meiringen, Meiringen, Switzerland; [6]Department of Psychosomatic Medicine and Psychotherapy, Otto von Guericke University Magdeburg, University Hospital Magdeburg; [7]Department for Clinical and Health Psychology, Wien University

Introduction: Stress has various negative effects on the body, both physically and mentally. Small and medium-sized enterprise (SME) leaders are particularly vulnerable to stress due to their demanding roles and responsibilities. A previous randomized controlled trail demonstrated beneficial effects of a 1.5 day stress intervention on circadian HRV parameters in a large company setting. The present RCT, funded by the Federal Ministry of Education and Research (BMBF), aims to replicate the effectiveness of a stress management intervention in reducing stress levels among small and medium-sized enterprise (SME) leaders and extend the findings to endocrine markers.

Method: Baseline biological measures were obtained from 135 participants, including 24-hour recordings of heart rate variability (HRV) using on channel EKGs and eight diurnal salivary alpha-amylase samples collected over two days. A second assessment was conducted 12 months later, with 93 participants available for analysis.

Results: Data analysis is currently ongoing and not yet complete. However, the study will report on the time-by-group interaction for circadian HRV (including cosine regression analysis) and diurnal salivary alpha-amylase patterns using linear mixed models.

Conclusion: Including circadian HRV and diurnal amylase levels as parameters in the study of stress management interventions provides valuable insights into their effectiveness at a physiological level. These biomarkers are highly sensitive indicators of the effects of stress on the body, allowing us to gain a deeper understanding of the impact of stress management training on the body's physiological response to stress.

PP19 Iron overload induces glucocorticoid resistance in mice

Rossana Paganoni, Peter Steele-Perkins, Maja Vujic Spasic

Ulm University, Germany

Background: Iron is an essential element for our body, with abnormal levels being related to chronic diseases such as thalassemia, sickle cell disease or multiple transfusions. Here excessive iron deposition in multiple tissues drives oxidative stress, inflammation, and alteration of their normal function. Macrophages represent one of the central cells in iron metabolism, as they orchestrate iron recycling from erythrocytes and redistribute iron. Glucocorticoids are the end targets of the HPA axis and regulate the immune response and metabolism of target cells through the activation of the glucocorticoid receptor (GR). Here, we investigate the effect of iron overload on glucocorticoid signaling through GR.

Methods: Mice were injected with Iron-dextran (1g/kg) once per week and sacrificed after 1 day and 8 weeks. Subsequently, the blood composition and iron parameters and GR activity were measured in the spleen.

Results: We show that 1 day of iron injection was sufficient to increase iron deposition in the spleen (2.3-fold increase, $p=0.0016$) and to significantly decrease Gr protein levels and its phosphorylated forms (pGrSer211 and pGrSer203). Chronically treated mice showed a similar phenotype: impairment of Gr signaling and its activity as a transcriptional regulator without changes in serum corticosterone levels (control 41.47±23.87 nmol/L, iron treated 44.05±17.99). Moreover, alternations in the composition of the white blood cells (i.e., lymphocytes, monocytes and granulocytes) were present, indicating possible alterations in immune status.

Discussion: Our findings imply that iron retention in macrophages is a driver of glucocorticoid resistance in mice, a condition that may be accompanied by underlying inflammation.

PP20 Inhibition of proinflammatory cytokines and chemokines in human neuroblastoma cells by cardenolides

Lu Sun, Adina Jeschor, Matthias Apweiler, Ashwini Tirkey

University of Freiburg, Faculty of Medicine, Germany

Chronic inflammation driven by proinflammatory cytokines such as Interleukin 6 (IL-6), Interleukin 8 (IL-8) and chemokines,such as chemokine (c-c motif) ligand (CCL2), plays an important role in the pathogenesis of several autoimmune, inflammatory as well as neurodegenerative disorders like Alzheimer's disease, multiple sclerosis, and Parkinson's disease. Therefore, identification of novel anti-inflammatory drugs may be beneficial for the treatment of disorders with a neuroinflammatory background. This study aimed to identify anti-inflammatory activities of various cardenolide derivates in interleukin-1beta (IL-1beta) stimulated SK-N-SH neuroblastoma cells and to further explore the underlying mechanisms of these activities. We investigated the anti-inflammatory activities by enzyme-linked immunosorbent assay (ELISA), quantitative polymerase chain reaction (qPCR), and Western blot (WB). We found anti-inflammatory effects by several of the cardenilde derivates on IL-6, IL-8, and CCL2 in IL-1beta treated SK-N-SH cells. The cardenolide derivatives X3362, X3363, X3350, X3378, X3312, X3381 showed inhibition of phosphorylated NF-kappa-B inhibitor alpha (IκB-α) and p65 NF.kappaB, and the degradation of IκBα. In addition, the cardenolide derivative significantly inhibited phosphorylated p38 (p-p38) mitogen activated protein kinase (MAPK). Based on those findings, we believe that those bioactive cardenolide derivative have the potential to be further developed as a potential therapeutic agent for inflammatory-related diseases.

PP21 Increased innate immune response and activated microglia in mice with genetically inherited low reactivity of the HPA axis

Kieron Knowles, Ahmet Gül, Leon Gohrbandt, Chadi Touma, Oliver Ambrée

Osnabrück University, Germany

Dysregulations of both, the immune system and the HPA axis have frequently been reported in patients suffering from stress-associated affective disorders such as major depression. The aim of the present study was to assess how extremes in HPA axis reactivity affect innate immune cell composition as well as microglia numbers and activation in mice.

Mice selectively bred for high, intermediate or low reactivity (HR, IR, LR) of the HPA axis were sacrificed at 6 months of age and spleens and brains were dissected. Splenocytes and microglia were isolated and analyzed by flow-cytometry. In addition, microglia activation was assessed morphologically on brain slices stained for Iba-1.

HR mice showed decreased numbers of CD11b+ myeloid cells and CD11c+ MHC class II+ dendritic cells compared to IR mice. LR mice, in contrast, presented increased numbers of CD11b+ myeloid cells producing the pro-inflammatory cytokine tumor necrosis factor and the anti-inflammatory cytokine interleukin-10. In addition, LR mice had significantly higher numbers of CD11b+ myeloid cells after LPS stimulation. LR mice also presented increased percentages of Ly6C+ as well as Ly6Chi and CCR2+ microglia. These cells showed larger cell bodies and shorter processes indicating an increased activation status of microglia in LR mice.

These results suggest that mice with low HPA axis reactivity have an activated innate immune response, indicating a relationship between HPA axis reactivity and innate immunity. Whether the activated immune response contributes to behavioral alterations such as reduced explorative behavior or passive stress-coping in LR mice has to be investigated in further studies.

PP22 Does redox dysregulation mediate the effects of childhood maltreatment on psychopathology?

Clara von Wendorff

Uniklinik Ulm, Germany

Background: Childhood maltreatment (CM) has a profound impact on mental health. Many studies have found a significant association between CM and activation of pathophysiological oxidative pathway. In addition, an increased level of redox markers appears to be associated with several psychiatric diagnoses (Ng, 2008). Redox dysregulation has been suggested as a pathway that may mediate the impairing effects of CM on mental health.

Objectives: This study aims to investigate the association of CMs, psychopathology, and redox markers in a high-risk sample of young adults who were previously placed in youth residential care institutions throughout Switzerland.

Method: Our sample includes 130 participants (30.8% women, M Age = 26.5 ± 3.7 years) with previous youth residential care placements (M Placements= 3.9). CMs and psychopathology were assessed with self-reported questionnaires and semi-structured clinical interviews. Redox dysregulation was measured using Superoxide dismutase (SOD), Glutathione peroxidase (GPx), Glutathione reductase (GRed), Peroxiredoxin 4 (PRX4), and Glutathione (GSH) in whole blood. Multivariate regression models were fitted to describe the associations between CMs, and psychopathology with redox markers, adjusting for covariates.

Results: 77.5% of participants screened positive for childhood adversity. 31% reported any psychopathology. A significant positive correlation was found between CM and psychopathology.

(the main results are not available yet and are expected in June 2023)

Conclusions: not yet available

PP23 Four week pet Exposure prevalence and urban vs. rural upbringing moderates the association between serum IL-6 and resting vagal activity – Evidence from a population based study

Marc N. Jarczok[1], Dominik Langgartner[2], Katja Weimer[1], Jonas Brunner-Weisser[2], Raphael Winkler[2], Harald Gündel[1], Stefan O. Reber[2]

[1]Department of Psychosomatic Medicine and Psychotherapy, Ulm University Medical Center, 89081 Ulm, Germany; [2]Laboratory for Molecular Psychosomatics, Department of Psychosomatic Medicine and Psychotherapy, Ulm University Medical Center, 89081 Ulm, Germany

Background: Own previous studies and unpublished data have demonstrated that rural vs. urban upbringing and presence vs. absence of own pets during urban upbringing is associated with differential inflammatory stress response patterns. The current study aims to replicate and extend these experimental findings from young males by investigating the effects of animal exposure frequency, urban vs. rural upbringing, and systemic inflammation in a large population sample.

Methods: Data on upbringing (rural vs. large-city), serum IL-6, animal exposure in the past 4 weeks prior to blood draw (no, yes), and resting vagal activity (HF-power), age and sex were analysed using bivariate Kendall-Tb and linear mixed models (LMM).

Results: The average age of participants was 56 years (54% female). IL-6 was negatively associated with HF-power and lower in participants with no recent animal contact vs with recent animal. Similar, participants raised in cities showed less association strength compared to rural upbringing. Results from LMM indicate an interaction between recent animal exposure and upbringing IL-6. Marginal mean prediction indicated a moderation between IL-6 and HF-power showing stronger negative associations for participants having animal contact, most pronounced in participants raised in rural areas.

Conclusions:

The present results extend previous findings that pets during urban upbringing can reduce the risk of developing stress-associated disorders later in life to the facet of recent animal contact and urban vs. rural upbringing and IL-6 as indicator of low-grade inflammation. The neuro-immunomodulatory association was stronger with recent animal contacts, indicating potential involvement of the cholinergic anti-inflammatory pathway.

PP24 Stress-induced alterations of peripheral macrophages and monocytes in susceptible and resilient mice

Marie Richter-Pezzullo[1,2], Rafael Leite Dantas[1,2], Oliver Ambrée[3], Marcel Marson[4], Anna-Lena Boller[1,2], Udo Dannlowski[1,5], Bernhard T. Baune[1,6,7], Stefanie Scheu[4], Judith Alferink[1,2]

[1]Department of Mental Health, University of Münster, Münster, Germany; [2]Cells in Motion (CiM) Interfaculty Centre, University of Münster, Münster, Germany; [3]Department of Behavioral Biology, University of Osnabrück, Osnabrück, Germany; [4]Institute of Medical Microbiology and Hospital Hygiene, University of Düsseldorf, Düsseldorf, Germany; [5]Institute for Translational Psychiatry, University of Münster, Münster, Germany; [6]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Australia; [7]Department of Psychiatry, The University of Melbourne, Melbourne, Australia

Background

Chronic stress associated with dysregulation of the innate immune system has been implicated in the pathophysiology of depression. Stress-induced alterations like altered percentages of macrophages, monocytes, and dendritic cells in lymphoid tissues have been found in mice. M1-macrophages are primarily associated with phagocytosis of pathogens and initiation of immune responses by production of proinflammatory cytokines, whereas M2-macrophages are linked to resolution of inflammation and tissue repair. In this study, we investigated the impact of stress on the immune system of mice, with a particular focus on M1 and M2 phenotype marker expression.

Methods

To induce stress, we exposed C57BL/6J mice to 10 days of social defeat stress. We evaluated behavioral and immune responses of chronically stressed mice compared to controls. By using flow cytometry and RT-PCR, the effect of stress on splenic and hippocampal T cells, B cells, dendritic cells, monocytes, and macrophages was investigated. Moreover, M1 and M2 phenotype marker expression and associated cytokine profiles were assessed.

Results

Our results demonstrate that social defeat stress led to increased depression-like behaviors and altered social interactions. All defeated mice showed reduced percentages of splenic CD11b+ MHC-II+ macrophages and CD11b+ Ly6C+ monocytes. More data regarding the specific immune phenotype of susceptible and resilient mice will be presented.

Conclusion

In this study, we characterized the phenotype of immune cells in response to chronic stress. Our data demonstrate specific changes of innate immune cells after social defeat stress. Additional analyses will be presented on immune cell profiles in stress-induced susceptibility and resilience

PP25 Characterization of the Impact of Childhood Trauma and Depression on Peripheral Blood Immune Signatures

Anna-Lena Boller[1,2], Jana Freff[1,2], Rafael Leite Dantas[1,2], Bernhard T. Baune[1,3,4], Tilo Kircher[5], Udo Dannlowski[6], Judith Alferink[1,2]

[1]Department of Mental Health, University of Münster, Münster, Germany; [2]Cells in Motion Interfaculty Centre, University of Münster, 48149 Münster, Germany; [3]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Australia; [4]Department of Psychiatry, The University of Melbourne, Melbourne, Australia; [5]Department of Psychiatry and Psychotherapy, University of Marburg, Germany; [6]Institute for Translational Psychiatry, University of Münster, Münster, Germany

Background: Major depressive disorder (MDD) is a severe mental disorder associated with alterations of the innate immune system. Childhood trauma (CT), an established risk factor of adulthood depression, also leads to chronic activation of peripheral immune cells. In this study, we investigated the association of specific immune cell types with childhood maltreatment and MDD, and their ability to predict depression severity.

Methods: Multiparameter flow cytometry was used to characterise immune cells in blood samples from age- and sex-matched individuals with MDD (n=47) and healthy controls (HC, n=53) from the FOR2107 consortium, which includes a maltreatment subgroup. The Hamilton Rating Scale for Depression (HAM-D) and the Childhood Trauma Questionnaire (CTQ) were used for stratification. Associations of specific immune cell types with CT and MDD were assessed. Regression analysis was used to determine the ability of immune variables to predict maltreatment experiences and severity of depression.

Results: In contrast to HC, patients with MDD exhibited reduced T cell and higher NK cell frequencies. While equivalent frequencies of B cells were found in MDD and HC, a positive correlation of these cells was found with sexual abuse in the whole group. NKdim cell frequencies, instead, were negatively correlated with physical and emotional neglect. Additionally, reduced T cell proportions were associated with physical and sexual abuse, and CTQ sum score. T cell frequencies together with CT status significantly predicted severity of MDD.

Conclusion: This immune signature and its ability to predict severity of MDD suggest a potential role in the pathophysiology of depression.

PP26 Effects of 10(Z)-hexadecenoic acid, a lipid isolated from Mycobacterium vaccae NCTC 11659, on murine bone marrow-derived dendritic cells: A mechanistic analysis

Elizabeth A. H. Hunter[1,2], Ian R. Rutherford[1], Caelan T. O. Wright[1], Evan M. Holbrook[3], Christopher A. Lowry[2,3]

[1]Department of Molecular, Cellular, and Developmental Biology, University of Colorado Boulder, Boulder, CO 80309, USA;; [2]Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, CO 80309, USA; [3]Department of Integrative Physiology, University of Colorado Boulder, Boulder, CO 80309, USA;

The “Old Friends” hypothesis proposes that people living in modernized societies have reduced exposure to diverse microbial communities present in the environment that promote immunoregulation. Mycobacterium vaccae NCTC 11659 is a soil-derived mycobacterium with anti-inflammatory and immunoregulatory effects. Some of these effects may be mediated by a lipid, 10(Z)-hexadecenoic acid (10(Z)-HDA), isolated from M. vaccae NCTC 11659. Studies have shown that 10(Z)-HDA acts as an agonist at the host peroxisome proliferator-activated receptor (PPARα) to induce anti-inflammatory effects in murine peritoneal macrophages. To determine if 10(Z)-HDA acts via PPARα to induce anti-inflammatory effects in dendritic cells, we conducted studies using 10(Z)-HDA and the PPARα antagonist GW6471 and assessed inflammatory biomarkers in murine bone marrow-derived dendritic cells (BMDCs) with or without subsequent immune challenge using lipopolysaccharide (LPS). Murine BMDCs were treated with two doses of GW6471 (0.24 μg/ml, 2.4 μg/ml) - or vehicle (1.5% DMSO), followed by 10(Z)-HDA at 250 μg/ml, or vehicle (13% DMSO, with a final well concentration of 0.5%). Twenty-four hours later, an immune challenge with LPS (Escherichia coli 0111:B4; 250 ng/ml) or vehicle was added. Cells were harvested 24 hours later and quantification of gene expression assessed using RT-PCR. After treatment with 2.4 μg/ml GW6471, relative to a vehicle-treated control condition, a significant decrease in Il6 expression following 10(Z)-HDA and LPS treatment was observed, suggesting that Il6 expression in murine BMDCs is controlled in part by PPARα. These results further our understanding of the mechanism by which 10(Z)-HDA has its effects and understanding of host mycobacteria interactions.

PP27 Effects of S1, a subunit of the spike protein of SARS-CoV-2, on the brain and behavior

Lyanna R Kessler, Matthew G Frank, Christopher A Lowry

University of Colorado Boulder, United States of America

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a strain of coronavirus that causes coronavirus disease 2019 (COVID-19), which resulted in a global pandemic. The spike protein of SARS-CoV-2 binds to the ACE-2 (angiotensin converting enzyme 2) receptor on host cells, which facilitates viral entry. Recent research has shown that the S1 subunit of the spike protein circulates in the bloodstream during infection and can bind to ACE-2 independently. Additionally, S1 can cross the blood-brain barrier and is associated with neuroinflammation in post-mortem human tissue and rodent studies. Here we compared humanized mice expressing human ACE-2, K18-hACE-2 mice, to wild-type mice, C57BL/6J. We also compared truncated S1 (RBD, just the receptor binding domain) to full-length S1 (FL-S1, which circulates during infection), since it is still unclear if RBD and FL-S1 have distinct functions. We applied 10 μg of RBD (three doses) or FL-S1 (single dose) via bilateral intranasal administration to determine if this can cause an increase in inflammatory gene and protein expression in the olfactory bulb, prefrontal cortex (PFC), and hippocampus. Our results show that RBD has a significant anti-inflammatory effect, evidenced by relative decreases in Itgam, Iba1, and Ifng gene expression in the hippocampus. Additionally, K18-hACE-2 mice had a stronger effect size than wild-type mice. We expect to continue to observe these anti-inflammatory effects of RBD in the olfactory bulbs and PFC, as measured by gene and protein expression. Based on previous studies, we expect FL-S1 will produce a strong proinflammatory effect, in contrast to RBD.

PP28 Brain insulin sensitivity is modulated by menstrual cycle

Julia Hummel[1], Charlotte Benkendorff[2], Louise Fritsche[3], Katsiaryna Prystupa[4], Andreas Vosseler[2], Sofiya Gancheva[4], Sandra Trenkamp[4], Andreas Birkenfeld[2], Hubert Preissl[3], Michael Roden[4], Hans-Ulrich Häring[2], Andreas Fritsche[2], Andreas Peter[2], Robert Wagner[4], Stephanie Kullmann[3], Martin Heni[1]

[1]Universitätsklinikum Ulm, Germany; [2]Universitätsklinikum Tübingen; [3]Helmholtz Zentrum München an der Universität Tübingen; [4]Deutsches Diabetes Zentrum, Düsseldorf

Background: Insulin action in the human brain modulates eating behavior, whole-body metabolism, and body fat distribution. Particularly, it increases whole-body insulin sensitivity, but these studies were mainly performed in lean men. We now investigated metabolic and hypothalamic effects of brain insulin action in women with a focus on the impact of menstrual cycle.

Methods and Results: Eleven women underwent four hyperinsulinemic-euglycemic clamps, two in the follicular and two in the luteal phase. Brain insulin action was introduced using nasal insulin spray. During the follicular phase, more glucose had to be infused after nasal insulin compared to placebo. This remained significant after adjustment for blood glucose and insulin. During the luteal phase, no significant influence of brain insulin action on glucose infusion rate was detected after adjustment for blood glucose and insulin. High estradiol/progesterone ratio, as present during the follicular phase, was linked to a stronger effect of insulin spray on glucose infusion rates than placebo.

In fifteen other women, hypothalamic insulin sensitivity was assessed by functional MRI with intranasal insulin. Hypothalamus responsivity was influenced by insulin in the follicular but not the luteal phase.

Conclusion: Hence, our study highlights that brain insulin action improves peripheral insulin sensitivity also in women, but only during the follicular phase. Thus, brain insulin resistance could contribute to whole-body insulin resistance in the luteal phase of the menstrual cycle.

PP29 Systemic administration of Fingolimod results in acute neurobehavioral changes in rats

Marie Jakobs, Lisa Trautmann, Stephan Leisengang, Manfred Schedlowski, Martin Hadamitzky, Laura Lückemann

Institute of Medical Psychology and Behavioral Immunobiology, Center for Translational and Behavioral Neurosciences (C-TNBS), University Hospital Essen, University of Duisburg-Essen, Essen, Germany

Background: Fingolimod (FTY720) is a functional antagonist of the sphingosine-1-phosphate receptor 1 (S1PR1). Under physiological conditions, the activation of S1PR1 by sphingosin-1-phosphate (S1P) leads to lymphocyte egress from the secondary lymphoid organs into the blood. However, when FTY720 binds to S1PR1 it causes internalization and degradation of the receptor. As a result, lymphocytes become unresponsive to S1P signals, preventing their egress from the secondary lymphoid organs, a condition known as lymphopenia. Interestingly, patients undergoing immunosuppressive therapy, including FTY720, often experience symptoms of affective disorders such as anxiety or depressive-like behavior. Since it is not clear whether the drugs themselves cause these symptoms, the present study analyzed the neurobehavioral effects of repeated FTY720 treatment in rats.

Methods: Male Dark Agouti rats were administered with a therapeutically effective dose of FTY (1mg/kg) systemically three times every 72 h. One hours following the last drug injection animals‘ behavioral performance in the elevated plus-maze test, the open-field test and the light-dark box was assessed.

Conclusion: Our study highlights the importance of investigating neurobiological mechanisms of action of immunosuppressive drugs frequently used in daily clinical routine. Analyzing the neurobehavioral effects of small-molecule immunosuppressive drugs may help to understand why and how these compounds induce central side effects