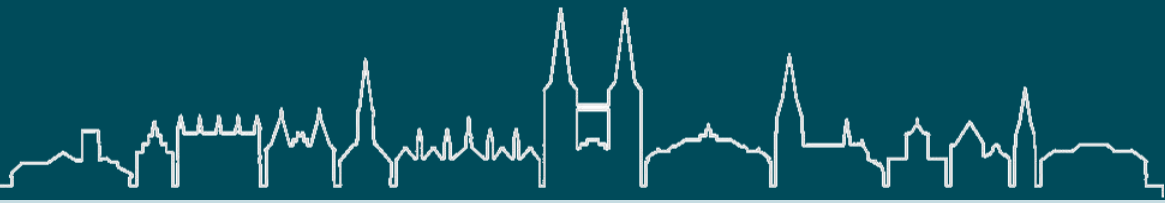
2nd ADIPOCYTE-BRAIN CROSSTALK SYMPOSIUM

March 14th – 15th 2019

Media Docks

Lübeck, Germany

ABSTRACT BOOK



UNIVERSITÄT ZU LÜBECK
GRK1957 | ADIPOCYTE-BRAIN CROSSTALK

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The voice for endocrinology


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Welcome in Lübeck
Greetings from the president of the University of Lübeck

Ladies and Gentleman, Dear Guests,

On behalf of the University of Lübeck I am delighted to welcome you to the "2nd Adipocyte-Brain Crosstalk Symposium" in Lübeck. This conference is based on the successful work of the Research Training Group 1957 which is directed by Professor Henrik Oster. It has been supported by the German Research Foundation since 2014 and is meanwhile in its second funding period.

My special appreciation goes to the doctoral students of this consortium, who organized this meeting, being responsible not only for the scientific program but also for all administrative issues related to such a conference.

The topic of this meeting is an integral and most significant part of "Brain, Behavior and Metabolism", one of the University's main research interests and I am really happy to see nationally and internationally renowned experts of this research area among the keynote speakers.

I wish all participants and especially also our foreign guests a successful symposium with fruitful and vivid scientific discussions. Enjoy the meeting but also the medieval history and charm of our beautiful hanseatic city!

Gillessen-Kaesbach

Prof. Dr. med. Gabriele Gillessen-Kaesbach
President of the University of Lübeck

Welcome in Lübeck
Greetings from the RTG-students

Dear participants and guests,

We are very pleased to welcome you to the 2nd Adipocyte-Brain Crosstalk Symposium in Lübeck. For the second time we, the students of the RTG 1957, organized this symposium completely by our own. That is why we are especially proud of welcoming you here in Lübeck.

In January 2018, we started planning and made many new, interesting and unique experiences. In addition to our normal work as PhD and MD students we organized not only the scientific program and invited our keynote speakers, searched and negotiated with sponsors, organized printing materials and catering.

We thank all of you for coming and for your participation and of course thanks to our sponsors, PIs and the University of Lübeck for providing support for this event. We hope that the upcoming two days will provide you a fruitful and interesting experience.

Best wishes,

students of the RTG 1957

Where to find us

By air

Lübeck is located approximately 60 km from Hamburg Airport.

The direct subway S1 takes you from Hamburg Airport (Terminal 1 underground) to the Hamburg Main Railway Station (Hbf).

Departure: every 10 minutes. Travel time: 25 minutes.

By train

From the Hamburg Main Railway Station you can take the RE train to Lübeck.

Departure: every 30 minutes. Travel time: 45 minutes

By bus

From the Lübeck city center and the Main Railway Station (http://www.sv-luebeck.de/en/)

Line 1, Stop *Wickedestraße*

Line 10, Stop *Wickedestraße*

Then walk 10 minutes

By car

The Media Docks are located close to the city center:

Willy-Brandt-Allee 31, entrance B

23554 Lübeck

Attendees of the symposium can park for free in front of the building.

Please send an email in advance to infoABC@uni-luebeck.de to request a parking space.

By foot

We highly recommend reaching the Media Docks by foot. It takes 15 minutes from Lübeck main station. It is only a 7 minute walk from the Radisson Blue hotel along the river side.

Media Docks
Willy-Brandt-Allee 31, entrance B
23554 Lübeck

Scientific Program

Thursday, March 14th 2019

13:00 – 14:00 **Registration**

14:00 – 14:15 **Welcome by Prof. Henrik Oster**

14:15 – 15:30 **Adipocyte-Brain Crosstalk**

Chairs: Dr. Henriette Kirchner & Prof. Hendrik Lehnert

14:15 – 14:45 **Keynote: Prof. Thorkild I.A. Sørensen**

Additional speakers:

14:45 – 15:00 **Dr. Ana Djordjevic**
The role of glucocorticoid signaling in rat visceral adiposity and hypothalamic appetite control after chronic stress

15:00 – 15:15 **Aleksandar Arsovic**
Dual control of nutrient metabolism in obesity and neurodegeneration by one protein: Ataxin-2

15:15 – 15:30 **Cathleen Geißler**
Development of hepatic insulin resistance is characterized by a metabolic switch

15:30 - 16:00 **Coffee break**

Thursday, March 14th 2019

16:00 – 17:15 Clocks in conflict: how time of feeding matters

Chairs: Prof. Henrik Oster & Dr. Violetta Pilorz

16:00 - 16:30 **Keynote: Prof. Andries Kalsbeek**

Additional speakers:

16:30 - 16:45 **Anne-Marie Neumann**
Modulation of behavioral and metabolic rhythms after bariatric surgery in mice

16:45 - 17:00 **Dr. Jana-Thabea Kiehn**
A role for circadian clocks in leptin-responsive neurons in appetite regulation in mice

17:00 - 17:15 **Dr. Sander Kooijman**
The circadian rhythm in glucocorticoids regulates brown adipose tissue activity

17:15 - 18:15 Poster session

Open end Dinner & get-together

Friday, March 15th 2019

08:30 - 09:00 **Welcome back – arrival and refreshments**

09:00 - 10:15 **Neurovascular unit in obesity: it's not all about neurons**

Chairs: Prof. Olaf Jöhren & Dr. Jan Wenzel

09:00 – 09:30 **Keynote: Dr. Cristina Gracía Cáceres**

Additional speakers:

09:30 – 09:45 **Sherif Idriss**
HIF-1α is stable and active in astrocytes under physioxia

09:45 – 10:00 **Elvira Sandin**
Tracing the transcytotic pathway of leptin across the blood-brain barrier

10:00 – 10:15 **Dylan Rausch**
Evidence of a key role for glial-neuron interactions underlying diabetes remission induced by fibroblast growth factor 1 (FGF1)

10:15 - 10:45 **Coffee break**

Friday, March 15th 2019

10:45 - 12:00 Beyond the hypothalamus: novel targets in obesity

Chairs: Dr. Carla Schulz & Prof. Nobert Brüggemann

10:45 – 11:15 **Keynote: Dr. Karolina Skibicka**

Additional speakers:

11:15 – 11:30 **Stephanie Kühne**
Nesfatin-130-59 injected intracerebroventricularly increases anxiety, depression-like behavior, and anhedonia in normal weight rats.

11:30 – 11:45 **Julia Steinhardt**
Body mass gain in Parkinson´s disease following deep brain stimulation: A systematic meta-analysis and preliminary study data

11:45 – 12:00 **Martina Obst**
Potential impact of long-term transcutaneous vagus nerve stimulation (tVNS) on metabolism and food intake behavior: an upcoming tool to control body weight?

12:00 - 13:00 **Lunch**

Friday, March 15th 2019

13:00 – 14:15 **BAT: the right kind of fat?**

Chairs: Prof. Jens Mittag & Prof. Sebastian Schmid

13:00 – 13:30 **Keynote: Prof. Camilla Charlotte Schéele**

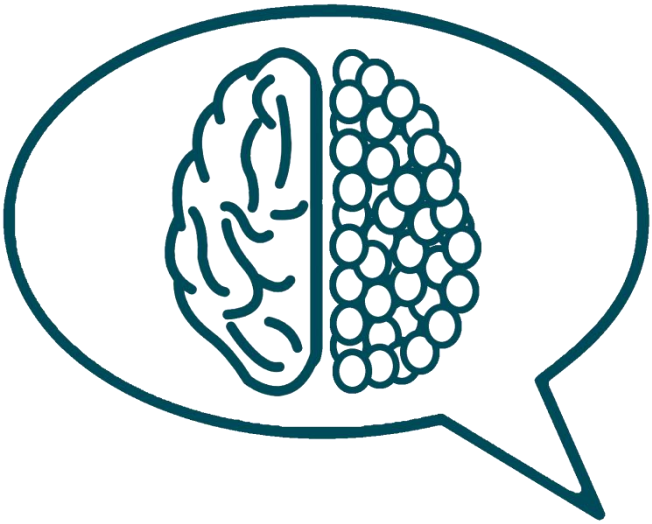
Additional speakers:

13:30 – 13:45 **Kornelia Johann**
Thyroid hormone induced browning of white adipose tissue does not contribute to thermogenesis

13:45 – 14:00 **Dr. Alexander Fischer**
De novo lipogenesis drives brown adipose tissue adaption to thermoneutrality

14:00 – 14:15 **Marius Richter**
Cerebral endothelial dysfunction alters metabolism and worsens hypercapnia-induced body temperature changes in mice

14:15 - 14:30 **Outro & farewell**



Adipocyte-Brain Crosstalk

The brain has a fundamental role in the regulation of energy homeostasis, exerting a rigorous control on body weight, appetite, and energy expenditure. Since the discovery of leptin and other adipokines, peripheral organs such as adipose tissue have gained equal importance in the regulation of obesity.

This session covers different aspects of the pathophysiology of obesity, including the close relationship between the brain and the adipose tissue.

Keynote: Prof. Thorkild I.A. Sørensen, Copenhagen

Keynote: Adipocyte-Brain Crosstalk

Adipocyte-Brain crosstalk in development of obesity?

Thorkild I.A. Sørensen[1]

[1] *Novo Nordisk Foundation Center for Basic Metabolic Research and Department of Public Health, Faculty of health and Medical Sciences, University of Copenhagen, Copenhagen Denmark*

In accordance with the energy balance equation, derived from the 1st thermodynamic law, development of obesity is usually considered to be caused by an energy intake that exceeds the energy expenditure. Although the energy balance is positive, it is a serious flaw to infer that it reflects a causal relation between increases in food intake in excess of the needs and subsequent passive deposition of the excess energy as fat in the adipose tissue. A primary tendency to excess accumulation of fat may well drive the process, leading to secondary adaptation of the energy balance to secure the energy supplies to the whole body, i.e. energy homeostasis for the remainder of the body. One of the strongest determinants of development of obesity is the psychosocial circumstances. While the prevailing view is that this is due to an excess in food intake, there are good reasons to be open to the possibility that the state of the brain, modulated by the psychosocial influences, directly drives on the development of obesity. This process may be regulated by a direct neuronal or neuro-hormonal cross-talk between the brain and the adipocytes.

Session: Adipocyte-Brain Crosstalk

The role of glucocorticoid signaling in rat visceral adiposity and hypothalamic appetite control after chronic stress combined with fructose-enriched diet

Ana Djordjevic[1], Biljana Bursać[2], Danijela Vojnović Milutinović[1], Ljupka Gligorovska[1], Nataša Veličković[1], Luc Tappy[3], Gordana Matić[1]

[1] Department of Biochemistry, Institute for Biological Research "Siniša Stanković", University of Belgrade, 142 Despot Stefan Blvd., 11000 Belgrade, Serbia; [2]CNRS, Institut de Biochimie et Génétique Cellulaires UMR5095, Université de Bordeaux, France; [3]Department of Physiology, University of Lausanne, UNIL-CHUV, Rue du Bugnon 7, CH-1005 Lausanne, Switzerland

Dietary fructose in combination with stress may contribute to dyslipidemia through deregulation of glucocorticoid signaling pathway in the visceral adipose tissue (VAT). Hypothalamus represents a hub of stress response and energy balance, since leptin and glucocorticoids regulate expression of orexigenic and anorexigenic neuropeptides in it. The aim was to assess the interaction of dietary fructose and chronic stress on VAT lipid metabolism and hypothalamic signaling in male Wistar rats.

We analyzed the effects of 9-week fructose diet and 4-week chronic stress, separately and in combination, on dyslipidemia, visceral adiposity and VAT histology and glucocorticoid signaling and expression of major metabolic genes. Hypothalamic glucocorticoid and leptin signaling and appetite control were also investigated.

Increased energy intake and higher blood triglycerides were observed in fructose-fed animals. VAT mass and adipocyte size were lower in stressed animals, which was congruent with decreased plasma leptin levels and hypothalamic expression of leptin receptor and suppressor of cytokine signaling 3. The combination of treatments was associated with higher plasma free fatty acids, paralleled with increased fatty acid synthase and acetyl-CoA carboxylase expression and stimulated glucocorticoid prereceptor metabolism in VAT. Anorexigenic neuropeptides – pro-opiomelanocortin and cocaine and amphetamine regulated transcript were decreased, while orexigenic agouti-related peptide was strongly upregulated in the same animals.

The results show that only combination of dietary fructose and stress increases glucocorticoid prereceptor metabolism and stimulates lipogenic enzyme expression in VAT, which is paralleled with orexigenic effect in the hypothalamus, suggesting that interaction between stress and dietary fructose may be instrumental in promoting VAT dysfunction.

Session: Adipocyte-Brain Crosstalk

Dual control of nutrient metabolism in obesity and neurodegeneration by one protein: Ataxin-2

Aleksandar Arsovic[1]*, Nesli Ece Sen[1]*, David Meierhofer[2], Isabel Lastres-Becker[1,3], Suzana Gispert[1], Georg Auburger[1]#

[1]Experimental Neurology Department, Universitätsklinikum Frankfurt, Frankfurt am Main
[2]Mass Spectrometry Facility, Max Planck Institute for Molecular Genetics, Berlin
[3]Department of Biochemistry, Faculty of Medicine, Universidad Autonoma de Madrid, Spain

Ataxin-2 was first identified as the monogenic cause of autosomal dominant spinocerebellar ataxia type 2, a progressive atrophy of the central nervous system primarily affecting cerebellum. While the unstable poly-glutamine (polyQ) expansion in the ATXN2 protein leads to insidious depletion of the peripheral fat stores in parallel to cerebellar neurodegeneration, the complete loss of Ataxin-2 interestingly triggers diabetes mellitus type 2 with insulin resistance, dyslipidemia, hepatosteatosis and obesity in mice. The physiological role of Ataxin-2 ranges from global translational regulation to receptor-mediated signaling and secretion. However, it is yet to be understood how the pathogenic polyQ expansion or the loss of Ataxin-2 leads to such distinct metabolic phenotypes. In order to understand the molecular mechanism underlying this phenomenon, we utilized two well-established mouse models of Ataxin-2 loss and pathogenesis; Atxn2-KO and Atxn2-CAG100-KnockIn. High-throughput proteome and metabolome analyses, together with expression data suggest that Ataxin-2 mainly regulates branched chain amino acid (BCAA) degradation and lipid metabolism in liver of both mutants, leading to altered membrane lipid composition in the cerebellum which is the primary site of degeneration in SCA2. Key enzymes in BCAA and lipid metabolism, such as BCKDH, BCKDK, PPM1K and ACLY have been found dysregulated in our mutants consistent with the phenotype they exert. All in all, Ataxin-2 emerges as an important modulator of basic metabolism in liver and brain, providing a potential therapeutic target to ameliorate both syndromes

Session: Adipocyte-Brain Crosstalk

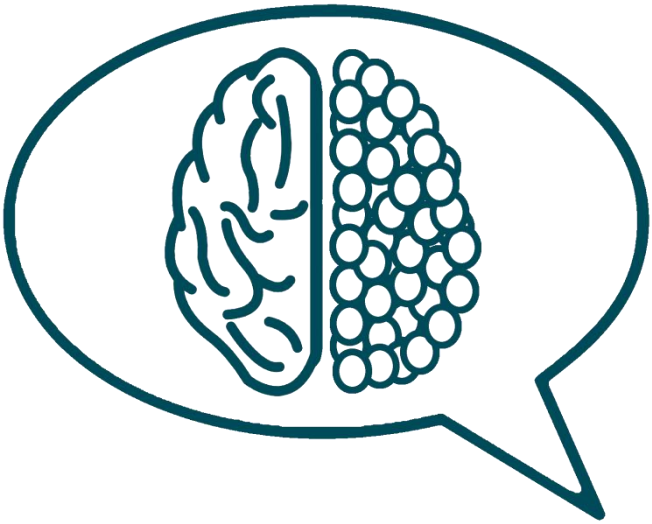
Development of hepatic insulin resistance is characterized by a metabolic switch

Cathleen Geißler[1], Christin Krause[1], Meike Kähler[2], Ingolf Cascorbi[2], Henriette Kirchner[1]

[1]Medical Department I, University of Lübeck, Lübeck, Germany
[2]Institute of Experimental and Clinical Pharmacology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany

Excess caloric intake leads to insulin resistance and hepatic fat accumulation, which is associated with altered expression of metabolically relevant genes. To determine whether these changes in gene expression are cause or consequence of hepatic insulin resistance we designed a longitudinal mouse experiment. Mice were fed with high fat diet (HFD) for up to 12 weeks and at five timepoints 8 mice of each group were sacrificed. Differentially regulated genes in early and late stages of hepatic insulin resistance were identified by transcriptome profiling. A metabolic switch occurs between week 4 and 8 of HFD feeding, thereafter mice are insulin resistant and fatty liver developed. Pathway analysis suggests an involvement of fatty acid metabolism and peroxisome proliferator-activated receptor (PPAR) signaling. In HFD-mice Ppara mRNA is significantly increased from week 4, whereas Pparg is significantly upregulated after 12 weeks. Genes of the lipogenesis are downregulated after 1 week of HFD. PPAR target genes regulating fatty acid oxidation are only slightly upregulated after 12 weeks in HFD-fed mice. Fgf21, a PPARa target gene known to be increased in NASH, is significantly upregulated as of week 4. First data indicate that DNA hypomethylation is likely causal for the vast increase in mRNA levels after 8 weeks of HFD. Although FGF21 as well as PPARs are thought to be protective against insulin resistance, their activation is not sufficient to rescue liver metabolism.

This work is supported by the Emmy-Noether-Program from the German Research Association (KI 1887/2-1)



Clocks in conflict: how time of feeding matters

Our central master clock, the suprachiasmatic nucleus (SCN), is synchronized by the 24-hour rhythm of light and darkness and communicates this information to various clocks throughout the body. However, the timing of food intake is able to regulate clocks in the periphery, particularly in metabolically active tissues, independent of the SCN.

This session focuses on the crosstalk of peripheral and central clocks in obesity, and the physiological consequences that derive from circadian conflict and desynchronization.

Keynote: Prof. Andries Kalsbeek, Amsterdam

Keynote: Clocks in conflict: how time of feeding matters

Clocks in Conflict: How Time of Feeding matters

Andries Kalsbeek[1]

[1] *Netherlands Institute of Neuroscience, Amsterdam, Netherlands*

Shift workers run an increased risk of developing metabolic disorders, presumably as a result of disturbed circadian physiology. Eating at a time-of-day that is normally dedicated to resting and fasting, may contribute to this association. According to the circadian desynchrony hypothesis, desynchrony between the various clocks in the circadian timing system and behavioral sleep/wake and fasting/ feeding rhythms may be involved in the pathophysiology of obesity and type 2 diabetes. Animals forced to eat at an unnatural time, i.e., during the light period, showed adverse changes in whole-body physiology and internal desynchronization of muscle and liver clock and metabolic gene expression. I will show several examples of how eating at the 'wrong' time-of-day causes internal desynchronization at different levels, which in the long run may disrupt body physiology.
In support of the circadian desynchrony hypothesis, the amplitude of rhythms of adipose clock gene expression is reduced in mouse models of type 2 diabetes. Despite this circumstantial support of the desynchrony hypothesis, the question of whether diurnal gene expression rhythms are altered in metabolic tissues of humans with type 2 diabetes remains to be answered. We therefore compared the in vivo diurnal gene expression rhythms in subcutaneous adipose tissue in obese individuals with type 2 diabetes vs healthy lean control individuals

Session: Clocks in conflict: how time of feeding matters

Modulation of behavioral and metabolic rhythms after bariatric surgery in mice

Anne-Marie Neumann[1], Cathleen Geißler[2], Henriette Kirchner[2], Henrik Oster[1]

[1] *Institut für Neurobiologie, Center of Brain, Behavior and Metabolism (CBBM), University of Lübeck, Germany*

[2] *Department of Internal Medicine 1: AG Epigenetics & Metabolism, University Hospital Lübeck*

Circadian clocks, the endocrine system and energy metabolism are tightly linked and mutually influence one another. Accordingly, chronodisruption is an increasingly recognized risk factor for obesity pathogenesis. After bariatric surgery, the most effective way to obtain long-term weight-loss, patients regain a healthier life style in regard to sleep and food intake rhythms. Still, outcomes vary and the underlying mechanisms remain largely unclear. After surgery, the endocrine and metabolic states change more rapidly and drastically compared to normal weight loss, potentially alternating circadian rhythms. It is tempting to speculate that circadian clocks affect the effectiveness of bariatric surgery.

Vertical sleeve gastrectomy (VSG) paradigms in rodents mirror the metabolic changes post-surgery in humans. We investigated surgical outcomes of VSG regarding food and activity rhythms under constant darkness conditions compared to sham-operated mice. Previously published data was reproduced showing a transient weight loss of maximal ~20% (n=13/8, RM-2-way-ANOVA). Additionally, locomotor activity and food intake pattern were altered. Moreover, in mice ubiquitary expressing luciferase fused with the core clock component PER2, we could demonstrate a phase-shift in the adrenal clock shortly after the surgery (n=6/5 slices, RM-2-way-ANOVA).

Conclusively, circadian clocks in the brain and the periphery appear to be sensitive to the metabolic alternations induced by bariatric surgery. We plan to further investigate gene expression and endocrine levels during the established “turning point” to improve understanding of the crosstalk between circadian clocks and metabolism and its role in weight loss therapies. The authors declare that there is no conflict of interest regarding the publication of this abstract

Session: Clocks in conflict: how time of feeding matters

A role for circadian clocks in leptin-responsive neurons in appetite regulation in mice

Jana-Thabea Kiehn[1], Christiane E. Koch[1], Laura Griewahn[1], Johanna L. Barclay[2], Henrik Oster[1]
[1] *Institute of Neurobiology, University of Lübeck, Lübeck, Germany*
[2] *University of Queensland, Brisbane, Queensland, Australia*

To anticipate and adapt to daily recurring events such as the light-dark cycle most species have developed internal, so called *circadian* clocks. In nocturnal rodents, like mice, food intake is high during the dark phase and low during the day, but clock gene disruption dampens this diurnal feeding rhythm. An important regulator of appetite is the adipocyte-derived hormone leptin, which acts on central appetite circuits *via* its receptor ObRb. Expression of *ObRb* mRNA shows a diurnal pattern, suggesting a reciprocal link between leptin-mediated control of energy homeostasis and central clock function. Therefore, we investigated the influence of circadian clocks in leptin-responsive neurons on energy homeostasis in ObRb.Bmal mice, in which the circadian clock was genetically ablated specifically in *ObRb*-positive neurons (ObRb.Cre x Bmal.flx/flx). On standard chow, ObRb.Bmal mice showed unchanged body weight and food intake. However, the circadian rhythm of *ObRb* expression and sensitivity to i.p. leptin was extinguished in ObRb. Bmal mice. Interestingly, the appetite for palatable food as well as palatable food-induced running-wheel activity was reduced during the day in ObRb.Bmal mice compared to control mice, suggesting an altered rewarding effect of energy-dense food. In summary, our data suggest that the molecular clock in *ObRb*-expressing neurons is involved in the circadian regulation of leptin sensitivity and has prominent effects on circadian regulation of food reward and hedonic appetite.

Session: Clocks in conflict: how time of feeding matters

The circadian rhythm in glucocorticoids regulates brown adipose tissue activity

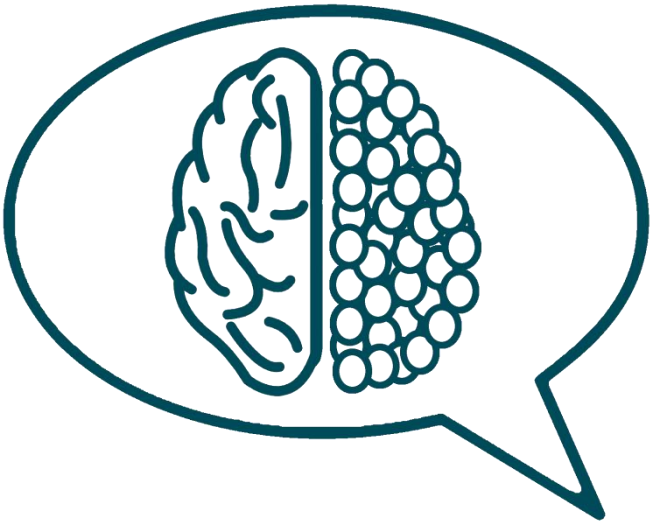
Schilperoort M, Kroon J, van den Berg R, Biermasz NR, Meijer OC, Rensen PCN, Kooijman S.[1]

[1]Department of Medicine, division of Endocrinology, Leiden University Medical Center, Leiden, Netherlands

Circulating levels of glucocorticoids display diurnal fluctuations, and are known to act as an internal synchronizer (or Zeitgeber) of many peripheral tissues. In this study, we explored whether the circadian rhythm of corticosterone (CORT) drives brown adipose tissue (BAT) activity and metabolic health in mice.

We first confirmed that the diurnality in plasma CORT levels closely resembles the rhythmic activity of BAT, i.e. the highest activity at the onset of the dark phase. Thereafter we equipped mice with pellets releasing a continuous low dose of CORT. The result was a flattened CORT rhythm accompanied by a loss of circadian rhythm in BAT activity. We subsequently explored the metabolic consequences of these flattened rhythms in APOE*3-Leiden.CETP mice as a model for hyperlipidemia and metabolic syndrome. After 5 weeks of intervention, flattened CORT increased fat mass (+2.8 g, $P<0.05$), and induced lipid accumulation in white adipose tissue (+65%, $P<0.01$) and BAT (+43%, $P<0.05$), while the uptake of fatty acids by BAT was reduced (-51%, $P<0.001$). To our surprise, rhythm in BAT activity was maintained in adipose-specific glucocorticoid receptor deficient mice, suggesting that CORT most likely regulates circadian BAT activity through crosstalk with the brain.

Collectively, these data indicate that CORT rhythmicity drives BAT activity, and that disturbance of this rhythm adversely affects metabolic health. As many individuals use synthetic glucocorticoids, this justifies further research on the interplay between glucocorticoids, BAT rhythm, and metabolic health in humans.



The neurovascular unit in obesity: It's not all about neurons

The role of non-neuronal cells in the modulation of metabolism and obesity has recently gained increasing attention. Endothelial cells and astrocytes of the neurovascular unit act to deliver cytokines, nutrients, oxygen and carbon dioxide; indirectly mediating neuronal activity in response to these. Tanycytes of the third ventricle have been implicated in multiple neuronal and metabolic functions, interacting directly with neurons and the neurovascular unit.

This session will pay special attention to the non-neuronal cell types, focusing on endothelial cells, astrocytes, and tanycytes; elucidating how they may in turn regulate neuronal activity and behavior related to obesity and metabolism.

Keynote: Dr. Cristina García Cáceres, Munich

Keynote: The neurovascular unit in obesity: It's not all about neurons

The neurovascular unit in obesity: It's not all about neurons

Cristina García Cáceres[1]

[1] *Institute for Diabetes and Obesity, Helmholtz Zentrum München, Germany*

Despite considerable efforts aimed at prevention and treatment, the prevalence of obesity, type 2 diabetes, and their comorbidities has increased at an alarming rate worldwide over recent decades. Given the urgent need to develop safe and efficient anti-obesity drugs, the scientific community has to intensify efforts to better understand the mechanisms involved in the onset of obesity. In the last decades, most research has been focused on solely exploring neuronal activity in order to understand how brain circuits control body weight, food intake, and energy balance, while ignoring the presence and active role of glia cells such as astrocytes. We have recently shown that astrocytes respond to circulating nutrients and hormones participating in glucose transport into the brain, and cooperate with neurons to efficiently regulate energy metabolism. Importantly, our studies were the first to show that astrocytes respond to hypercaloric diets by developing a reactive phenotype -astrogliosis- in the hypothalamus, which appears prior to significant diet-induced body weight gain, suggesting the potentially functional role of these glial cells in the pathogenesis of obesity. Overall, our recent findings suggest a novel model in which astrocytes are actively involved, together with neurons, in the central nervous system control of systemic metabolism.

Session: The neurovascular unit in obesity: It's not all about neurons

Activation of HIF-1α and differential regulation of its target genes in astrocytes under physioxia

Sherif Idriss[1], Silje Zimek[1], Katia Monsorno[1,2], Olaf Jöhren[1]

[1] Institute of Experimental and Clinical Pharmacology and Toxicology, Center of Brain, Behavior and Metabolism (CBBM), University of Lübeck, Germany

[2] University of Trento, Italy

The physiological levels of oxygen (physioxia; 3-5% oxygen in brain) are significantly lower than oxygen levels (21%) in the air (normoxia) due to the decrease in blood oxygen levels across the lung and to organs throughout the body. Oxygen levels below the physiological range (hypoxia; 1% Oxygen) can result in disturbed physiological functions leading to injury. In response to hypoxia, Hypoxia Inducible Factors (HIFs) are activated, stabilized; HIF-1/2α enter the nucleus, where they heterodimerise with HIF-1β and bind to a DNA sequence known as the hypoxia responsive element (HRE), modulating transcription of HIF target genes such as glucose transporter 1 (GLUT1), phosphofructokinase (PFK) and lactate dehydrogenase A (LDHA), monocarboxylate transporter 4 (MCT4).

We investigated whether HIF-1α is stabilised in primary astrocytes by NO under physioxia as we have shown before for normoxia. We also aimed to estimate whether HIF-1α is active under physioxia without further stimulation by NO. Cortical astrocytes obtained from 1 day old pups in primary culture are treated with nitric oxide donor DetaNONOate (Deta) and HIF-1α was knocked down by siRNA independently under normoxia, physioxia and hypoxia. HIF-1α and HIF-1α target gene expression was analysed at mRNA and protein levels by RT-qPCRs and Western blots respectively.

Results: HIF-1α is not only active under normoxia but also at physioxia by Deta treatment. Following HIF-1α knockdown, MCT4 is selectively downregulated but not GLUT1 or HK.

Conclusions: Under physioxia HIF-1α is activated and HIF-1α target genes are differentially regulated.

Session: The neurovascular unit in obesity: It's not all about neurons

Tracing the transcytotic pathway of leptin across the blood-brain barrier

Elvira Sandin, Markus Schwaninger[1]

[1] Institute of Experimental and Clinical Pharmacology and Toxicology Center of Brain, Behavior and Metabolism (CBBM), University of Lübeck, Germany

Treating obesity is one of the paramount challenges in western society. At the discovery of leptin, a highly potent satiety inducing hormone, hopes were high that treatment with leptin itself would be able to combat obesity. However, it was quickly discovered that obese individuals are resistant to the satiety inducing effects of leptin, and have elevated levels of circulating leptin. Part of the resistance to leptin is mediated by reduced transport rate of leptin through the blood-brain barrier (BBB) into the regions of the brain where this adipokine acts to reduce hunger. Therefore, understanding the transport of leptin into the brain may present attractive targets for treating obesity. To elucidate the intracellular and receptor mediated mechanisms underlying leptin transport through the BBB we have established and optimized a primary porcine brain cortical endothelial cell culture (pBCEC), and a luciferase linker fusion protein wherein Gaussia luciferase (Gluc) is linked to leptin. We have been able to show that this fusion protein is able to activate the leptin receptor and exhibits flash luciferase activity similar to Gaussia luciferase. We expect that these tools enable the molecular analysis of leptin transport across the BBB.

Session: The neurovascular unit in obesity: It's not all about neurons

Evidence of a key role for glial-neuron interactions underlying diabetes remission induced by fibroblast growth factor 1 (FGF1)

Dylan Rausch, Marie Aare Bentsen, Zaman Mirzadeh, Ken Muta, Jarrad Scarlett, Jenny Brown, Jonatan Thompson, Kimberly Alonge, Vicente Herranz-Perez, Karl Kaiyala, Cecilia Friis Ratner, Birgitte Holst, Thomas Meek, Burak Kutlu, Thomas Sparso, Gregory Morton, Jose-Manuel Garcia-Verdugo, Anna Secher, Rasmus Jorgensen, Tune Hannes Pers, Michael W. Schwartz[1]

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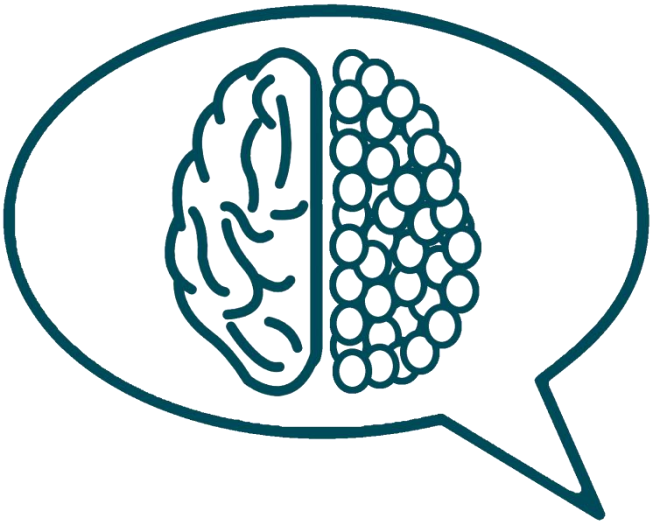
Lasting remission of hyperglycemia can be achieved in rodent models of type 2 diabetes (T2D) by a single intracerebroventricular (icv) injection of fibroblast growth factor 1 (FGF1), and the mediobasal hypothalamus (MBH) has been identified as a target for this effect. To investigate cellular and molecular mechanisms underlying FGF1 action in the MBH, we combined whole tissue RNA-sequencing with large-scale single cell and single nuclei RNA-sequencing to identify and characterize FGF1-responsive cells in mouse MBH. Based on >60,000 single cell transcriptomes from diabetic ob/ob mice harvested 5d after a single icv injection of either FGF1 or vehicle, distinct gene modules correlating with icv FGF1 treatment were identified primarily in neurovascular cells, astrocytes, tanycytes and microglia. Such modules were notably absent from neurons, in which the transcriptomic response to FGF1 was suggestive of global neuronal inhibition. Among neuron-specific genes inhibited by FGF1 is Agrp, which is overexpressed in the hypothalamus of diabetic ob/ob mice, and is implicated in the pathogenesis of diabetic hyperglycemia. Using a combination of methods, we show that Agrp neuron inhibition occurs rapidly following icv FGF1 injection and persists for at least 6 wk. We also show that the resultant increase of hypothalamic melanocortin signaling (Agrp is an endogenous antagonist of melanocortin receptors) is required for the sustained glucose-lowering effect of icv FGF1 injection. Although the mechanism underlying sustained Agrp neuron inhibition following icv FGF1 injection remains unclear, the astrocyte response to FGF1 closely paralleled the neuroprotective "A2" transcriptional phenotype that is predicted to inhibit neuron activity. FGF1-responsive glial cells may therefore underlie the persisting inhibition of MBH neurons that drives sustained diabetes remission.



Beyond the hypothalamus: Novel targets in obesity

The hypothalamus is classically defined as the main brain area for the control of energy balance, regulating both energy intake and energy expenditure. However, a growing body of evidence is suggesting the previously unknown involvement of other brain regions, as well peripheral signals, in the regulation of energy homeostasis and obesity.

This session focuses on novel regions, compounds, and mechanisms in the regulation of energy balance, and in the development and maintenance of obesity.

Keynote: Dr. Karolina Skibicka, Gothenburg

Keynote: Beyond the hypothalamus: Novel targets in obesity

A gut feeling, as dictated by sex and neuroanatomy

Karolina Skibicka[1]

[1] *Department of Physiology at Institute of Neuroscience and Physiology*

All aspects of feeding behavior are under tight control of the central nervous system. In recent years important strides in understanding the neural circuitry controlling feeding behavior were made. Yet, this circuitry has largely been investigated in male animals. This trend is perfectly mirrored by literature exploring the food intake and reinforcement impact of gut peptides, including glucagon-like peptide (GLP-1). Nonetheless, recent data suggest that neural control of appetite and reward may differ between males and females, and therefore results obtained from male animals are not necessarily readily applicable to females. Moreover, sex steroid receptors are found in nearly all brain nuclei directly responding to gut signals, creating neuroanatomical and molecular conditions for direct interactions of these signals. In my talk, I will explore how sex, and sex steroids alter food reinforcement effects of GLP-1, and discuss how these interactions differ as a function of neuroanatomical location. I will show both quantitative and qualitative differences between male and female responses to central GLP-1R manipulations, highlighting the importance of including both sexes in preclinical studies of food reward.

Session: Beyond the hypothalamus: Novel targets in obesity

Nesfatin-130-59 injected intracerebroventricularly increases anxiety, depression-like behavior, and anhedonia in normal weight rats

Stephanie Kühne[1], Martha Anna Schalla[1],Tiemo Friedrich,[1] Peter Kobelt[1],Miriam Goebel-Stengel[1,2,3] ,Melissa Long,[4] Marion Rivalan[4], York Winter,[4] Matthias Rose[1],and Andreas Stengel[1,3]

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[4] Cognitive Neurobiology, Berlin Mouse Clinic for Neurology and Psychiatry, Humboldt University, 10117 Berlin, Germany

Nesfatin-1 was discovered as an anorexigenic peptide in the rat hypothalamus in 2006. Recently, an association between nesfatin-1 and anxiety and depression has been observed. However, it is still unclear whether this effect persists under obese conditions. Therefore, this study aimed to explore the impact of the active core of nesfatin-1, nesfatin-130-59, on anxiety, anhedonia and depression-like behavior in normal weight (NW) and diet-induced (DIO) obese male rats. After intracerebroventricular (icv) cannulation rats were injected with nesfatin-130-59 (0.1, 0.3, or 0.9 nmol/rat) or vehicle 30 min before testing. Nesfatin-130-59 at the medium dose (0.3 nmol) reduced sucrose intake in the sucrose preference test in NW rats compared to vehicle (-33%, $p < 0.05$), suggesting that nesfatin-130-59 induced depression-like/anhedonic behavior. This dose was used for all following experiments. Additionally, during the novelty-induced hypophagia test nesfatin-130-59 significantly reduced cookie intake (-62%, $p < 0.05$). Furthermore, nesfatin-130-59 reduced the number of entries into the center zone in the open field test (-45%, $p < 0.01$) in NW rats pointing towards anxious/depressive-like behavior. In the elevated zero maze test the visits of open arms (-39%, $p < 0.01$) were significantly reduced in NW rats after icv injection of nesfatin-130-59, further supporting the idea of an anxiogenic effect of the peptide. Interestingly, no behavioral changes were observed in DIO rats after icv injection of nesfatin-130-59 ($p > 0.05$). These results indicate an implication of nesfatin-130-59 in the mediation of anxiety and depression-like behavior/anhedonia under normal weight conditions, while in DIO rats a desensitization might occur. The authors declare no conflicts of interest.

Session: Beyond the hypothalamus: Novel targets in obesity

Body mass gain in Parkinson´s disease following deep brain stimulation: A systematic meta-analysis and preliminary study data

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Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a well-established therapy in advanced Parkinson's disease (PD) for managing severe motor complications. However, a remarkable weight gain has been consistently reported after STN-DBS surgery, which - at least in part – counteracts the positive effects of motor improvement.
Methods: For this systematic review and meta-analysis, a computerized search for relevant articles was performed in MEDLINE, Cochrane Library, Clinical Trials, and Livivio against a priori inclusion/exclusion criteria. Main outcome parameters were body weight and body mass Index (BMI). Effect size was calculated by Cohens' d.
Results: 38 out of 154 studies were included in this meta-analysis with a total sample size of 979 patients and follow-up time between 1 and 60 months after surgery. Mean age across studies was 59.0±7.5 years. Over all studies, mean weight gain for the longest follow-up period in each study was 5.2 kg ($p<0.0001$) with corresponding effect size of $d=0.64$. For BMI, mean increase over all studies was 1.8 kg/m2 ($p<0.0001$; $d=0.78$). Prior to STN-DBS surgery, 40% of the patients were overweight. After surgery, this proportion increased up to 78%. Body weight increased continuously within the following time intervals: +2.9 kg ($d=0.69$) at 3 months, +3.9 kg ($d=0.216$) at 6 months, +6.4 kg ($d=0.72$) at 12 months, and +6.3 kg ($d=1.02$) at >12 months, respectively, after surgery.
Conclusion: In view of negative health implications of weight gain, the development of tailored therapies to prevent obesity and accompanied metabolic disorders after STN-DBS surgery is required.

Session: Beyond the hypothalamus: Novel targets in obesity

Potential impact of long-term transcutaneous vagus nerve stimulation (tVNS) on metabolism and food intake behavior: an upcoming tool to control body weight?

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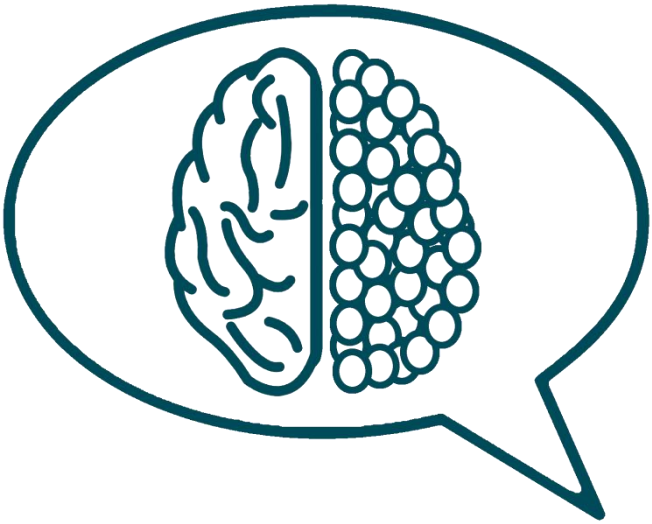
One of the most pressing health problems, at least in developed countries, is the obesity epidemic. Up to now, behavioral interventions and pharmacological treatments show limited effectiveness, are costly or burdened with side effects. Brain stimulation techniques could represent an alternative to the current treatments. In particular, stimulation of the vagus nerve - the so-called gut-brain axis - is promising because it is a core component in the regulation of body weight and of eating behaviour. Indeed, evidence exists from animal models and from the treatment of patients with epilepsy or major depression, that stimulating the vagus nerve via implanted electrodes (VNS) has a profound impact on food consumption behavior, metabolism and body weight. However, in contrast to previous studies, the present investigation used a transcutaneous vagus nerve stimulation (tVNS) and tested its potential impact on the regulation of body weight.
In a pre-post study design, 34 healthy, male subjects with a Body Mass Index (BMI) ≥ 27 kg/m2 received either a tVNS or a sham stimulation at the left outer ear over 5 weeks. Despite body weight and body height, additionally metabolic (blood parameter, basal metabolic rate (BMR), body composure), neuronal (resting state-MRI, functional MRI) and behavioral parameters (wanting/liking, approach-avoidance tendencies) were collected enabling the investigation of interactions across systems.
Particularly, first results to its effects on the food approach-avoidance behaviour (AAT task), the neuronal activity and blood parameter are presented.
Finally, preliminary conclusions are drawn, and further planned analysis are outlined.



BAT: The right kind of fat?

Brown adipose tissue (BAT) is known to be the main site of adaptive thermogenesis in mammals, acting to maintain core body temperature by burning metabolic substrates. Boosting energy expenditure by stimulating BAT activity seems to be promising as therapeutic strategy to tackle obesity and metabolic abnormalities. However, several aspects on molecular mechanism controlling energy expenditure and BAT activation are still unclear.

This session aims to further elucidate BAT physiology and function as well as mechanisms involved in thermogenesis and energy metabolism, with a special focus on the neuroendocrine pathways controlling cold-induced BAT activity.

Keynote: Prof. Camilla Charlotte Schéele, Copenhagen

Keynote: BAT: The right kind of fat?

The plasticity of human brown adipose tissue

Camilla Charlotte Scheele[1]

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Brown adipose tissue (BAT) of adult humans is complex and appears as a mixture of unilocular and multilocular adipocytes. We mapped the adipocyte morphology along with the abundance of the major BAT marker, mitochondrial uncoupling protein 1 (UCP1) in the perirenal BAT. This depot consists of active BAT during childhood and is interesting to study due to its proximity to the catecholamine-producing adrenal gland. We found an asymmetric distribution of multilocular adipocytes near the adrenal gland, whereas distant regions consisted of unilocular but UCP1-positive cells, which we propose to be dormant BAT. Transcriptomic analysis revealed that this dormant BAT is an intermediate between multilocular BAT and white adipose tissue (WAT). Dormant BAT seems to be present in other depots, including the supraclavicular deep neck region where we found that obesity accelerated dormancy. Importantly, regardless of depot, brown preadipocytes were present in dormant BAT biopsies and could differentiate into functional brown adipocytes in vitro, providing an avenue for reactivation of BAT, which could be beneficial for counteracting obesity and its related diseases. From a larger perspective, our studies illustrates that the plasticity of adipose tissue is not limited to WAT accumulating BAT-like heat-producing properties in response to cold but expands to BAT gaining WAT-like energy-storing properties in association with obesity

Session: BAT: The right kind of fat?

Thyroid hormone induced browning of white adipose tissue does not contribute to thermogenesis

Kornelia Johann[1], Anna Lena Cremer[2], Sebastian Nock[1], Alexander Fischer[3], Markus Heine[3], Sam Virtue[4], Lisbeth Harder[1], Rebecca Oelkrug[1], Georg Brabant[1], Miguel Lopez[5,6], Amy Warner[7], Antonio Vidal-Puig[4], Joerg Heeren[3], Jeffrey W. Dalley[8,9], Heiko Backes[2], Jens Mittag[1]

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Regulation of body temperature critically depends on thyroid hormone (TH). Recent studies revealed that TH activates brown fat thermogenesis and induces browning of white adipose tissue, possibly contributing to the observed hyperthermia in hyperthyroid patients and potentially providing favourable metabolic effects. In this study, we show that browning of white fat by TH requires TH receptor beta and likely occurs independently of the sympathetic nervous system, as it is still observed at thermoneutrality with minimal norepinephrine stimulation. Despite high levels of uncoupling protein 1 (UCP1), both, brown and beige fat of hyperthyroid mice are not metabolically active, as glucose and lipid uptake are decreased. Most importantly, the metabolic and thermogenic effects of the hormone were maintained in hyperthyroid UCP1-knockout mice, demonstrating that they do not require brown or beige fat, respectively. Skeletal muscle of hyperthyroid mice showed decreased glycogen content, as well as increased lipid uptake, indicating an increased metabolic rate, possibly contributing to the observed hyperthermia. Our findings clarify the mechanisms contributing to hyperthermia in systemic hyperthyroidism and underline that the mere presence of UCP1 is insufficient to draw conclusions on its activity and the therapeutic potential of a browning agent. The authors declare no conflict of interest.

Session: BAT: The right kind of fat?

De novo lipogenesis drives brown adipose tissue adaption to thermoneutrality

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Cold-induced activation of brown adipose tissue (BAT) protects from obesity, diabetes and atherosclerosis. Conversely, thermoneutral housing results in diminished non-shivering thermogenesis and in brown fat whitening, a process leading to a metabolic switch from oxidative metabolism towards lipid storage. Interfering with this adaptation might be therapeutically relevant for preservation of BAT oxidative metabolism at thermoneutral temperatures representing standard human living conditions.

Here we show that de novo lipogenesis (DNL) is a major mechanism driving BAT whitening, which we target genetically and pharmacologically to preserve the beneficial effects of BAT activity in the absence of cold stimulus.

To identify the source of the lipids accumulating in BAT during whitening, we performed lipidomic analyses, uncovering increased levels of DNL-derived lipids in major lipid classes in thermoneutral BAT. We identified carbohydrate response element-binding protein (ChREBP) as the main driver of DNL in BAT. Interestingly, mice lacking ChREBP globally and specifically in brown adipocytes were resistant to thermoneutral housing, as loss of ChREBP not only abolished thermoneutrality-induced lipid accumulation, but also preserved mitochondrial mass, UCP1 levels and oxidative capacity in BAT. Mechanistically, alterations in anabolic signaling cascades initiate whitening in wild type, but not ChREBP-deficient BAT. ChREBP-dependent DNL fueled both lipid storage as well as intracellular phospholipid pools in BAT. Alterations in the lipid composition drove mitochondrial breakdown and reduction in oxidative capacity at thermoneutrality.

In summary, we demonstrate a vital role of ChREBP in the cellular adaption of BAT to thermoneutrality. In light of the metabolically harmful outcome of BAT deactivation at thermoneutral housing, targeting whitening through inhibition of DNL may represent a new approach to either preserve or boost BAT function and its beneficial effects on metabolism.

Session: BAT: The right kind of fat?

Cerebral endothelial dysfunction alters metabolism and worsens hypercapnia-induced body temperature changes in mice

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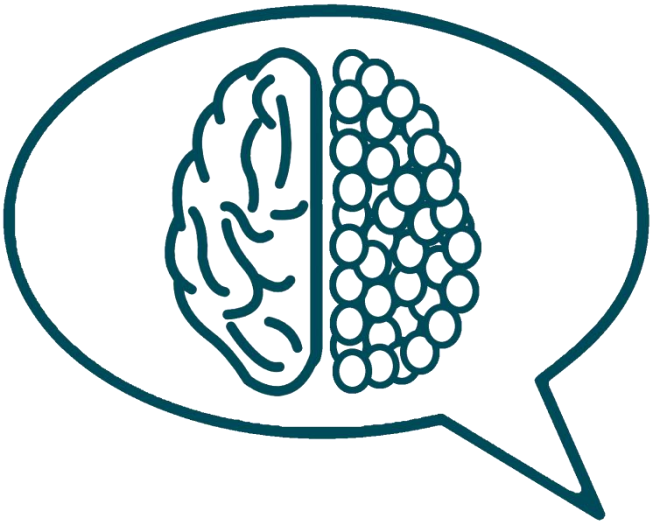
More than 40% of obese patients develop obstructive sleep apnea and endothelial dysfunction as a secondary symptom. Obstructive sleep apnea is associated with hypercapnia. In endothelial dysfunction vessels fail to respond to stimuli (e.g. CO2) that normally trigger vasodilation or vasoconstriction. How the pathological changes, obstructive sleep apnea and endothelial dysfunction, affect each other or the underlying metabolic changes, is unknown so far. Our study addresses the question, whether cerebral endothelial dysfunction itself or together with hypercapnia alters metabolism and might promote pathological changes. For that purpose we use a Gαq/11 brain endothelial knockout (Gαq/11beKO) mouse model to mimic cerebral endothelial dysfunction. We observed a 12.5% reduction in energy expenditure and a 28.6% increase in body fat in Gαq/11beKO mice in comparison to controls. To model hypercapnia, we exposed Gαq/11beKO and control mice to elevated CO2 levels (10%) in the ambient atmosphere for a short period (10 minutes). Using thermography, upon CO2 exposure we observed a dramatic decrease of brown adipose tissue temperature in Gαq/11beKO mice compared to controls, revealing differences in body temperature regulation. The body temperature itself decreased only in Gαq/11beKO mice but not in controls. The data show that cerebral endothelial dysfunction itself has an effect on the metabolism and that together with hypercapnia, dramatic changes in body temperature occur. We speculate that the hypothalamus, as a central regulatory region of body temperature and metabolism, plays an important role in the altered regulation and that this effect is mediated by the brown adipose tissue.



Poster Session

March 14th, 17:15-18:15

Poster Session

A1 - Resting energy expenditure in Parkinson's Disease: A cross-sectional study – Preliminary results

Laura Lokowandt [1], Julia Steinhardt [1,2], Sebastian M Schmid [2,3], Thomas F Münte [1,4], Britta Wilms [2,3]*, Norbert Brüggemann [1,4]*

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Background: Parkinson's Disease (PD) is associated with changes in body mass. While many patients lose weight under medical treatment, PD patients often gain weight after deep brain stimulation (DBS) surgery. Since resting energy expenditure (REE) accounts for up to 70% of 24h-energy expenditure the quantification of REE is a crucial step in understanding mechanisms of weight change in PD. We aim to assess REE in PD patients in comparison to healthy controls.
Methods: REE and respiratory quotient (RQ) were measured by indirect calorimetry in 21 PD patients (5 women), and 19 control subjects (9 women). In addition, body composition and MDS-UPDRS III were assessed. In order to compare REE between groups the percent of predicted REE (%REE) was calculated (Müller et al, AJCN 2004).
Results: Age, body mass, and BMI were comparable between groups (all $p>0.124$). As expected, the PD group showed much higher values in MDS-UPDRS III than the CON group ($p<0.001$). Absolute REE (1466+/-57 vs. 1364+/-44 kcal/d) and %REE (88.6+/-1.9 vs. 88.7+/-1.4 %) were not different between groups (both $p>0.140$). In line, RQ (0.81+/-0.01 vs. 0.79+/-0.01) and heart rate (64.3+/-1.4 vs. 64.5+/-2.2 bpm) were comparable (both $p>0.333$).
Discussion: Our data show no evidence for alterations in REE in PD and thus, disease severity of e.g. motor symptoms was not reflected by altered REE. Therefore, we speculate that body weight gain after DBS is driven by either decreased activity related energy expenditure or changes in energy intake. Our longitudinal study may provide data relevant for answering this research question.

Poster Session

A2 - A novel psychological program leads to sustained weight loss and improves body composition, satisfaction with oneself, body image, and stress hormone levels

Juliane Richter[1], Sophia Moenikes[1], Kai Duysen[1], Kerstin M. Oltmanns[1]
[1] Center of Brain, Behavior and Metabolism, University of Lübeck, Lübeck, Germany

Conventional approaches for body weight loss are not successful in the long term. This failure additionally reinforces a negative body image and self-dissatisfaction resulting in increased stress levels, which in turn impedes weight loss. In a prospective intervention study, we examined the long-term effectiveness of a novel three months learning program for weight reduction applied by a smartphone app (NUPP). Moreover, potential effects on psychological factors and stress hormone concentrations, which hamper weight loss, were investigated.

Over a study period of six months, 75 obese subjects (BMI 35.4 ± 0.5 kg/m2; age 50.1 ± 1.6; 55 % female) were examined four times (program start, after one month, program ending, and six months after onset). Body weight and composition, stress hormone levels, as well as satisfaction with oneself and body image were determined over the entire period.

There was a significant body weight ($p = 0.011$) and BMI ($p = 0.012$) reduction associated with an increase in muscle-fat mass ratio ($p = 0.003$). Both ACTH and cortisol concentrations decreased during the study ($p < 0.002$ for both). Subjects were significantly more satisfied with themselves ($p = 0.001$) and perceived their body image as less negative ($p = 0.006$).

A novel smartphone-based learning program leads to sustained weight loss and improves body composition. Moreover, the program ameliorates psychological and endocrine factors, which hamper successful weight loss in the long term, thereby breaking the vicious circle of unsuccessful weight loss, dissatisfaction, and stress.

There are no conflicts of interest to declare.

Poster Session

A3 - Obese Zucker rats after experiencing a Roux-en-Y gastric bypass surgery or calorie restriction: An expression study in the heart and various brain regions

Anja Hock[1], Paula Arias-Loza[2,3] Sophie Heiser[1], Gabriela Ortega[1], Jürgen Deckert[1], Florian Seyfried[4], Theo Pelzer[1], Bodo Warrings[1], Angelika Schmitt-Böhrer[1]

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[3] Comprehensive Heart Failure Center, University Hospital Würzburg, Würzburg, Germany

[4] Department of General, Visceral, Vascular and Pediatric Surgery, University of Würzburg, Germany

Obesity and its associated diseases like diabetes type 2, cardiovascular disease and dementia represent a major health burden. While conservative treatments often fail to work, bariatric surgery is an effective weight-loss procedure. Although its positive effect is incompletely understood, hormonal and neuroendocrine changes are suggested to be causative. The "Wuerzburg Adipose Rodent Study" uses Zucker rats to study the effects of Roux-en-Y gastric bypass (RYGB) surgery and calorie restriction on obesity and cardiac function. The study design comprises four groups: Zucker lean rats sham-treated, Zucker rats sham-treated, Zucker rats RYGB treated, and Zucker rats sham-treated with a calorie reduced diet. Applying an insulin signaling pathway RT2 ProfilerTM PCR array revealed expression differences of some of those genes such as Igf1 in heart tissue. To investigate the expression of insulin signaling pathway-related genes in the brain of these rats, we performed qPCR using RNA from hypothalamus, hippocampus, prefrontal cortex and striatum. Heart RNA was analyzed as additional control and to verify originally obtained results. We detected significantly reduced expression levels of Irs1, Igf1 and Insr in the heart of Zucker compared to Lean rats. RYGB and calorie restriction did not reverse this effect. In the brain, we did not detect expression differences at all with exception of Akt2. However, the investigation of other energy homeostasis-related genes such as the adiponectin receptor 1 are still ongoing. No conflict of interest exists.

Poster Session

A4 - Amplitude of brain signals classify metabolic state (hunger/ satiety) based on machine learning in resting-state fMRI

Arkan Al-Zubaidi, Alfred Mertins, Marcus Heldmann, Kamila Jauch-Chara, Thomas F. Münte[1]

[1] Dept. of Neurology, University of Lübeck; Institute for Signal Processing, University of Lübeck
[2] Institute of Psychology II, University of Lübeck
[3] Dept. of Psychiatry and Psychotherapy, Christian-Albrechts-University

Resting-state fMRI (rs-fMRI) is a method of functional brain imaging that allows the task-free exploration of the intrinsic functional connectivity in humans. Since central nervous pathways regulate food intake and eating behavior, it is assumed that changes in the homeostatic state have an impact on the connectivity patterns of rs-fMRI. Here, we compare the accuracy of three data-driven approaches in classifying two metabolic states (hunger vs. satiety) depending on the observed rs-fMRI fluctuations. These methods assess local and global functional connectivity as well as amplitude (intensity) fluctuations of neural signals: First, regional homogeneity (ReHo), which describes the synchronization of time series of a given voxel and its nearest neighbors. Second, the degree of centrality (DC), which measures the number of connections of a voxel to all the other voxels above a certain threshold. Third, the fractional amplitude of low-frequency fluctuation (fALFF), which measures voxel-wise signal amplitude. After extracting the associated connectivity parameters of 90 brain regions for each method, we use features selection algorithms with the objective function of linear support vector machine classifier and permutation tests to investigate which method and which brain regions differentiate best between hungry and satiety. Our results indicate that the fALFF method is more accurate than ReHo and DC in capturing the changes of the resting brain during states of hunger and satiety. This opens up the possibility to use this measure to characterize certain states (e.g., sleep stages) or disease conditions (e.g., mitochondrial encephalopathy).

Poster Session

A5 - Data-driven discovery of energy homeostasis regulating pathways in the hypothalamus

Mette Ludwig, Pascal Timshel, Dylan Rausch, Jonatan Thompson, Tune H Pers[1]

[1] Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen

The large gap in understanding obesity prevents effective prevention and therapy. Studies on human body mass index (BMI) genetics have emphasized the role of the brain in obesity pathogenesis and obesity is now recognized as a disease of the energy homeostasis regulating system. The hypothalamus has been identified as an integrating master regulator of this system. Only recently the full heterogeneity of the hypothalamic cell populations has started to be explored using the single-cell RNA-sequencing technology which provides new opportunities to discover novel pathways of the energy homeostasis system. The aim of this study is to map the human BMI genetic signal to cell type specific pathways in the hypothalamus. By integrating four single-cell transcriptomics data sets from the hypothalamus of mice exposed to different feeding conditions, we identified common hypothalamic cell types. We detected pathways specific to cell types with weighted gene co-expression network analysis follow by Gene Ontology and KEGG enrichment analysis. By integrating these pathways with BMI genetic association data, we established the importance of cell type specific pathways in human obesity. We found that pathways specific to neurons and tanycytes were associated with BMI genetic signal. Surprisingly, a coherent pathway response to either high fat diet or fasting was not evident across the data sets.

Poster Session

A6 - Development of hepatic insulin resistance is characterized by a metabolic switch

Cathleen Geißler[1], Christin Krause[1], Meike Kähler[2], Ingolf Cascorbi[2], Henriette Kirchner[1]

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[2] Institute of Experimental and Clinical Pharmacology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany

Excess caloric intake leads to insulin resistance and hepatic fat accumulation, which is associated with altered expression of metabolically relevant genes. To determine whether these changes in gene expression are cause or consequence of hepatic insulin resistance we designed a longitudinal mouse experiment. Mice were fed with high fat diet (HFD) for up to 12 weeks and at five timepoints 8 mice of each group were sacrificed. Differentially regulated genes in early and late stages of hepatic insulin resistance were identified by transcriptome profiling. A metabolic switch occurs between week 4 and 8 of HFD feeding, thereafter mice are insulin resistant and fatty liver developed. Pathway analysis suggests an involvement of fatty acid metabolism and peroxisome proliferator-activated receptor (PPAR) signaling. In HFD-mice Ppara mRNA is significantly increased from week 4, whereas Pparg is significantly upregulated after 12 weeks. Genes of the lipogenesis are downregulated after 1 week of HFD. PPAR target genes regulating fatty acid oxidation are only slightly upregulated after 12 weeks in HFD-fed mice. Fgf21, a PPARa target gene known to be increased in NASH, is significantly upregulated as of week 4. First data indicate that DNA hypomethylation is likely causal for the vast increase in mRNA levels after 8 weeks of HFD. Although FGF21 as well as PPARs are thought to be protective against insulin resistance, their activation is not sufficient to rescue liver metabolism.

This work is supported by the Emmy-Noether-Program from the German Research Association (KI 1887/2-1)

Poster Session

B1 - Circadian changes in the dopaminergic system after hedonic food intake

Kimberly Begemann, Christiane E. Koch[1], Jana-Thabea Kiehn[1], Andreas Moser[2], Henrik Oster[1]

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To anticipate and adapt to external environmental rhythms such as the light-dark cycle, most organisms developed intrinsic timekeepers, so-called circadian clocks. However, rhythm disturbances, such as mistimed food intake, desynchronise this endogenous clock network and thereby promote hedonic food overconsumption and obesity. Interestingly, dopamine levels in the nucleus accumbens (NAc) were found to be increased in response to a food or drug reward, suggesting an influence of the clock on hedonic feeding rhythms. Additionally, daily oscillations of NAc dopamine levels imply an influence of the clock on the reward system.

We hypothesised a regulation of hedonic appetite rhythms by circadian controlled dopamine release in the NAc. Using intracranial microdialysis to detect and quantify dopamine release directly in the NAc of mice and combining it with an associated analytical method we characterised snack-induced changes in NAc dopamine levels. The quantified concentrations were significantly higher in the beginning of the active phase compared to the beginning of the rest phase ($p=0.0098$), in line with published data. Additionally, we could show significantly higher snack-induced increases in NAc dopamine levels during the rest phase ($p=0.0286$) as well as alterations in locomotor activity. Summarised, we show that time-of-day dependent chocolate consumption leads to a circadian controlled response in NAc dopamine release which may be involved in the regulation of hedonic appetite rhythms. Behavioural therapies of body weight regulation could therefore consider the avoidance of hedonic overconsumption.

The authors declare no conflict of interest.

Poster Session

B2 - Adipokine regulation of circadian clocks in hypothalamic neurons

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Numerous studies have shown that chronodisruption, which can be caused by shiftwork, represents a risk factor for the development of metabolic disorders. Furthermore, food intake during the normal rest phase promotes obesity, showing that there is an association between timing of food intake and body weight homeostasis. Interestingly, high-fat diet access has been shown to disrupt diurnal feeding patterns and clock gene expression in the mediobasal hypothalamus (MBH). These data suggest an important function of metabolic endocrine signaling in regulating diurnal feeding behavior. However, which signals relay the metabolic state to central circadian circuits is still poorly understood. Since MBH nuclei integrate peripheral metabolic signals to adjust appetite, we hypothesize that adipokine feedback signals modulate MBH clocks to regulate diurnal feeding rhythms. Using a combination of cell and tissue explant cultures as well as genetic and pharmacological manipulations in mice, we are investigating the communication between adipose tissues and central circadian clocks in mice. Using immortalized hypothalamic cell lines, we are screening for metabolic feedback signals capable to modulate MBH clocks and characterize their role in the modulation of feeding rhythms.

Poster Session

B3 - Regulation of circadian behavior and metabolism by melatonin

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The rotation of the earth around its axis generates a 24h daily rhythm, to which behavior and physiological functions of almost every living organism are adjusted to. A central pace maker in the suprachiasmatic nucleus (SCN) synchronizes other central and peripheral clocks partly with messenger molecules. One of these messenger molecules is the hormone melatonin, which I will focus on in my research. Melatonin is mainly produced in the pineal gland and has a synchronizing function on circadian rhythms. Its sleep-promoting function is already used for therapeutic approach. The effect of melatonin is relayed via the G protein-coupled melatonin receptors MT1 and MT2. Via these receptors melatonin affects not only circadian rhythms, but also the immune system and metabolism. C57BL/6J mice have a lack of a key enzyme, regulating melatonin production in the pineal gland. Even though these mice are not able to produce functional melatonin, MT1 and MT2 receptors are still expressed, so that this model is suitable for manipulation and experiments with melatonin supplementation. By rhythmic melatonin substitution, the natural rhythm is mimicked and the synchronizing effect on central and peripheral tissue clocks as well as on metabolism and behavior is investigated. My experiments will include short time trials to discover the acute effect of this hormone as well as a long-term experiments that will concentrate on metabolic development in body composition, glucose and energy homeostasis. No conflict of interest to declare.

Poster Session

B4 - Circadian rhythms of hedonic appetite in ob/ob mice

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To anticipate and adapt to daily recurring events such as the light-dark cycle most species have developed internal, so called circadian clocks. Circadian clocks regulate rhythmic behavior, including homeostatic and hedonic feeding rhythms. Disruption of diurnal feeding rhythms disturbs energy homeostasis and promotes body weight gain. An important regulator of appetite and energy homeostasis is the adipokine leptin. Leptin is encoded by the obese (ob) gene. Ob transcription is controlled by circadian clocks and food intake, leading to higher serum levels during the night in mice. Leptin acts in the mediobasal hypothalamus, where it reduces homeostatic appetite and stimulates energy expenditure. Additionally, it reduces hedonic appetite via its action in the mesolimbic dopaminergic reward system. Although it has been shown that leptin plays an important role in the circadian regulation of homeostatic appetite, so far it is not known if it also affects circadian rhythms of hedonic appetite. To study the role of leptin in circadian rhythms of hedonic appetite regulation, we studied intake rhythms in ob/ob mice carrying a loss-of-function mutation in the obese gene. We hypothesized that leptin deficiency in these mice results in altered hedonic appetite rhythms. 24-hour profiles of hedonic liquid overconsumption of ob/ob mice were analyzed using lickometer cages where mice had the choice between hedonic 10-% sucrose solution and plain water. Besides, we investigated diurnal rhythms of hedonic snack intake and hedonic snack-induced neuronal activation in the mesolimbic dopaminergic reward system.

Poster Session

B5 - Palmitate changes circadian clock gene expression in hypothalamic cells

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The external light-dark cycle synchronizes our bodies' circadian clocks to anticipate daily environmental changes and organize physiological functions accordingly. Food intake during the resting phase can disturb the circadian system and lead to obesity. Obese patients suffer from heavily altered lipid profiles. Among the free fatty acids, palmitate is the most abundant in blood as well as Western style diets. It was shown to disrupt clock rhythms and cellular functions of hepatocytes and β-cells. We hypothesize, that diurnal metabolic signals such as palmitate may not only affect peripheral tissues but also clocks in central food regulatory centers. To test this, we used immortalized mouse hypothalamic neuronal cells and investigated the effect of palmitate on clock gene mRNA transcription. Supplementation of 2mM palmitate induced expression of Bmal1 (after 8h $p<0.001$), Per2 ($p<0.001$), Rev-Erbα ($p<0.01$) while Clock was unaffected. The potential BMAL1 regulator, Pgc1α, was also acutely increased. In synchronized cells, rhythms of Bmal1 and Clock mRNA as well as the expression of Pparα and Pgc1α were altered by 1mM palmitate. To evaluate the effect of palmitate on rhythmicity, the cells were robustly transfected to express the luciferase reporter enzyme under the control of the Bmal1-promotor. In summary, we were able to show the rhythm altering potential of specific dietary fatty acids on hypothalamic clocks. These data may help to understand the pathogenesis of obesity better and find ways to stop the vicious cycle of chronodisruption and dysfunctional energy metabolism. The author declare not conflict of interest.

Poster Session

C1 - Mice develop endothelial dysfunction upon long-term high fat diet

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Obesity and the associated metabolic syndrome are raising problems in developed countries and treatment options are still insufficient. Beyond blood pressure regulation, there is strong evidence that the renin angiotensin system (RAS) is linked to both glucose control and obesity. Commonly used angiotensin 1 (AT1) receptor blocker, such as telmisartan, has shown to prevent rodents on the one hand from diet induced obesity (DIO) and on the other hand to improve their metabolic status. Hyperglycemia as wells as obesity are also associated with a reduced cerebral blood flow (CBF), which might be related to an exacerbation of cerebrovascular rarefaction and neurovascular uncoupling. Here, we investigated whether stimulated CBF and neurovascular coupling (NVC) is impaired after high fat diet (HFD) feeding and whether HFD worsen spatial memory forming. Furthermore, we wanted to know whether telmisartan can recover these parameters in obese mice. Upon 8 weeks of HFD, we couldn't see a difference in CBF or NVC between lean and obese mice. Moreover, lean mice didn't show better spatial memory testing performance compared to their littermates with DIO. Consequently, telmisartan didn't have a positive effect on NVC and memory upon 8 weeks of treatment. Therefore, we fed mice for a longer time period with HFD. Upon 16 weeks, obese mice developed cerebral endothelial dysfunction. The cerebrovascular reaction upon whisker stimulation was on the one hand decreased by 18.4 % and on the other hand decelerated by 0.3 sec.

Poster Session

C2 - Functional identification of G protein-coupled receptors in murine tanycytes

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The neural network of the hypothalamus is responsible for energy balance and it controls several hormonal axes. For this, it is necessary to detect and integrate different neural and metabolic signals and thus to determine the energy and hormone status of the organism. The described network is remarkably regulated by tanycytes, specialized glial cells in the wall of the third ventricle, which are important for release and uptake of biologically active substances in this area. However, it is not fully understood to what extent tanycytes are able to sense different compounds and how their signal is transmitted. It is known that thyrotropin-releasing hormone and carbachol elicit Ca2+-signalling, while forskolin increases cAMP via a G protein-coupled pathway in subpopulations of these cells. The aim of this study is to find new agonists or antagonists of G protein-coupled receptors that modulate tanycytic function. To visualise Ca2+ or cAMP levels specifically in tanycytes, adeno-associated virus containing a fluorescent Ca2+ or cAMP sensor are injected into the lateral ventricle of mice. Using fluorescence microscope equipped with high speed calcium imaging setup, compounds are tested on acute brain slices of these transduced mice. Our preliminary results show that two new compounds increase Ca2+ levels in tanycytes: 18:1 lysophosphatidic acid, acting on lysophosphatidic acid receptors and ATI-2341 via chemokine receptor 4.

Poster Session

C3 - Possible effects of renin angiotensin system compounds on the leptin transport across the blood brain barrier in vitro

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Obesity is a global and growing health problem and treatment options are still not available. When chronically treated with a angiotensin II receptor typ 1 (AT1) blocker (ARB), rodents do not develop diet-induced obesity. Consequently, we assume that the beneficial effects of ARBs on food intake and body weight are at least partly mediated via the leptin signaling cascade. However, the underlying mechanism for this is still unclear. Here we investigated the effects of angiotensin II and the ARB losartan on leptin uptake across the blood brain barrier (BBB) in vitro.

After we have identified the hCMEC/D3 cell line as a suitable BBB cell model in terms of integrity and leptin and AT1 receptor expression, we treated cells in a transwell system with either angiotensin II, losartan or both.

In general we could not show a clear effect of the two compounds of the renin angiotensin system (RAS) on the transport of leptin through the cell barrier, but we could see a time dependent trend towards an impaired transport upon the treatment with angiotensin II and a restored transport by losartan after two hours, which we could not see after 90 min. We also could show that the transport of leptin was about 10-fold improved by the pretreatment with dexamethasone due to an increased leptin receptor expression.

As there are no consistent effects of angiotensin II or losartan on the leptin transport, we conclude that these compounds are not directly involved in an altered BBB permeability in obesity

Poster Session

C4 - Activation of HIF-1α and differential regulation of its target genes in astrocytes under physioxia

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The physiological levels of oxygen (physioxia; 3-5% oxygen in brain) are significantly lower than oxygen levels (21%) in the air (normoxia) due to the decrease in blood oxygen levels across the lung and to organs throughout the body. Oxygen levels below the physiological range (hypoxia; 1% Oxygen) can result in disturbed physiological functions leading to injury. In response to hypoxia, Hypoxia Inducible Factors (HIFs) are activated, stabilized; HIF-1/2α enter the nucleus, where they heterodimerise with HIF-1β and bind to a DNA sequence known as the hypoxia responsive element (HRE), modulating transcription of HIF target genes such as glucose transporter 1 (GLUT1), phosphofructokinase (PFK) and lactate dehydrogenase A (LDHA), monocarboxylate transporter 4 (MCT4).

We investigated whether HIF-1α is stabilised in primary astrocytes by NO under physioxia as we have shown before for normoxia. We also aimed to estimate whether HIF-1α is active under physioxia without further stimulation by NO. Cortical astrocytes obtained from 1 day old pups in primary culture are treated with nitric oxide donor DetaNONOate (Deta) and HIF-1α was knocked down by siRNA independently under normoxia, physioxia and hypoxia. HIF-1α and HIF-1α target gene expression was analysed at mRNA and protein levels by RT-qPCRs and Western blots respectively.

Results: HIF-1α is not only active under normoxia but also at physioxia by Deta treatment. Following HIF-1α knockdown, MCT4 is selectively downregulated but not GLUT1 or HK.

Conclusions: Under physioxia HIF-1α is activated and HIF-1α target genes are differentially regulated.

Poster Session

C5 - Lipidomics analysis of plasma and brain tissue of LRP2beKO mice by LC-MS/MS

Julica Folberth, Alessandro Di Spiezio, Elvira Sandin, Alaa Othman, Markus Schwaninger[1]

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LRP2 (low density lipoprotein receptor-related protein 2) is a membrane spanning receptor that has been shown to transport, among others, several Apolipoproteins. We hypothesized that a brain endothelial cell specific knockout of LRP2 (LRP2beKO) leads to changes in the lipid metabolism. Lipidomics can be defined as a comprehensive analysis of lipid species in a biological system. Tandem mass spectrometry (MS/MS) is the method of choice for lipidomics analysis, the identification based on specific fragmentation patterns and prior separation of the lipids via liquid chromatography (LC MS/MS) increases selectivity and the level of identification confidence. Preliminary studies with LRP2beKO mice showed changes in calorimetric parameters and confirmed alterations of the lipid metabolism. In detail, lipidomics analysis of over 230 lipid species revealed an increase in six sphingomyelin species in the brain (Hypothalamus)/plasma ratio and a decrease in seven further sphingomyelin species in the plasma. Four phosphatidylcholine and two lysophosphatidylcholine species were decreased in the plasma of the LRP2beKO animals as well. No changes were detected in brain tissue from the cortex or the VTA. To confirm and extend these preliminary results, further calorimetric and mass spectrometry based experiments are planned.

Poster Session

C6 - Hyperglycemia-induced α-dicarbonyls in diabetes-related vascular dementia

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Diabetes mellitus is the most common metabolic disorder in humans, approaching epidemic proportions with increasing incidence and prevalence over the last decades. Besides well described long-term complications like nephro-, neuro- and retinopathy, chronic hyperglycemia additionally displays a strong correlation with the development of dementia. Although it is well established that chronic hyperglycemia leads to vascular complications and cerebral microinfarcts, the molecular basis of the development of cognitive impairment due to diabetes is still unclear. A possible link between the increased blood sugar and the degenerating vascular system could be the production of highly reactive and toxic metabolites of glucose. Hence, we investigated the production of a distinct class of such molecules, which share an α-dicarbonyl structure, and their effect on the cerebrovascular system. Therefore, diabetes was induced in C57BL/6 mice by injecting 50 mg/kg streptocotocin on 5 consecutive days. After 14 weeks, mice were tested for cognitive impairment by an object-place recognition test. Afterwards mice were sacrificed for staining of the vascular system and detection of α-dicarbonyls by mass spectrometry. We provide evidence that chronic hyperglycemia leads to an increase of α-dicarbonyls in blood plasma and brain tissue of diabetic mice which additionally showed signs of cognitive decline in an object place recognition test (OPRT). This result was associated with an increase of 4-hydroxynonenal positive vessels, indicating oxidative stress. Further analysis of the vascular system revealed higher abundance of string vessels, reflecting the degeneration of the vascular integrity. Furthermore, we could verify the induction of oxidative stress in endothelial cells in vitro.

Poster Session

C7 - Tracing the transcytotic pathway of leptin across the blood-brain barrier

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Treating obesity is one of the paramount challenges in western society. At the discovery of leptin, a highly potent satiety inducing hormone, hopes were high that treatment with leptin itself would be able to combat obesity. However, it was quickly discovered that obese individuals are resistant to the satiety inducing effects of leptin, and have elevated levels of circulating leptin. Part of the resistance to leptin is mediated by reduced transport rate of leptin through the blood-brain barrier (BBB) into the regions of the brain where this adipokine acts to reduce hunger. Therefore, understanding the transport of leptin into the brain may present attractive targets for treating obesity. To elucidate the intracellular and receptor mediated mechanisms underlying leptin transport through the BBB we have established and optimized a primary porcine brain cortical endothelial cell culture (pBCEC), and a luciferase linker fusion protein wherein Gaussia luciferase (Gluc) is linked to leptin. We have been able to show that this fusion protein is able to activate the leptin receptor and exhibits flash luciferase activity similar to Gaussia luciferase. We expect that these tools enable the molecular analysis of leptin transport across the BBB.

Poster Session

C8 - Endothelial dysfunction and its effect on sleep and CO2-induced arousal in mice

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Impaired cerebrovascular reactivity due to endothelial dysfunction is a known consequence of the metabolic syndrome. Physiologically, cerebral perfusion differs in sleep from waking state but mechanisms remain unknown. An eligible marker for cerebrovascular reserve is the response to CO2 as it is a strong stimulus for hyperperfusion in cortical areas. In addition, CO2 promotes arousal from sleep and is an important breathing stimulus. The Gαq/11 pathway in brain endothelial cells was found to play a major role in CO2-induced hyperperfusion. Thus, to investigate the consequences of impaired cerebrovascular reactivity, a mouse model with a brain endothelial deletion of Gαq/11 (Gαq/11beKO) was chosen for further investigations. The aim is to find out how impaired cerebrovascular reactivity affects sleep architecture and CO2-induced arousal in mice. Epidural EEG and EMG electrodes are implanted surgically into Gαq/11beKO and control mice and recording takes place for 24h. To measure CO2-induced arousal we built a glass chamber containing two gas connectors for inflow and outflow, an airtight cable port for EEG- and EMG recordings and hygroscopic flooring. Mice are adapted to the recording chamber for several days prior to measurements that take place during inactive (day) time. Inflow of 10% CO2 commences after 1 minute of sleep monitoring and time until arousal from sleep is recorded in EEG and EMG data. The results will be compared between control and Gαq/11beKO mice. Diseases that are associated with endothelial dysfunction are known to induce alterations in sleep. Results may help to improve understanding of the contributing mechanisms.

Poster Session

D1 - Importance of the paraventricular nucleus of the hypothalamus for the anorexigenic and thermogenic effects of NUCB2/nesfatin-1

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Nesfatin-1, a potent regulator of energy homeostasis, derives from the precursor nucleobindin-2 (NUCB2), and is widely expressed in both the periphery and central nervous system incl. the paraventricular nucleus of the hypothalamus (PVN), which has been proposed to have a major role in mediating nesfatin's effects. To further investigate the homeostatic role of NUCB2/nesfatin-1 in the PVN, in male rats, this nucleus was either unilaterally cannulated to allow nesfatin-1 or nesfatin-1-antibody (Nes1-Ab) administration, or bilaterally injected with an adeno-associated virus carrying a shRNA to knockdown NUCB2 gene expression. Acute intra-PVN administration of nesfatin-1 decreased dark-phase food intake ($p<0.001$) over 6h; increased dry heat loss (DHL) ($p<0.05$) over 8h, measured via direct calorimetry; and increased brown adipose tissue temperature (PBS: +0.6°C; nesfatin-1: +1.33°C; $p<0.01$) over 1.5h, assessed by infrared thermography. These data underline the fundamental role of the PVN in exerting NUCB2/nesfatin-1 effects. Conversely, blockade of endogenous nesfatin-1 via Nes1-Ab decreased DHL ($p<0.05$) and increased food intake ($p<0.05$) up to 24h. Similarly, chronic PVN-specific knockdown of NUCB2 expression increased daily food intake ($p<0.05$), particularly during the late light-phase ($p<0.01$), and lowered DHL (~-15%, $p<0.001$), leading to ~+10% gain in body weight of knockdown animals, due to an increase in fat mass by ~+36% compared to ~+9% in controls. Overall, our findings provide a better perspective on the role of both endogenous and exogenous PVN NUCB2/nesfatin-1 in the regulation of energy homeostasis. Ongoing experiments aim to clarify the role of other energy homeostasis-related brain regions, and the downstream mediators recruited by nesfatin-1.

Poster Session

D2 - Potential impact of long-term transcutaneous vagus nerve stimulation (tVNS) on metabolism and food intake behavior: an upcoming tool to control body weight?

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One of the most pressing health problems, at least in developed countries, is the obesity epidemic. Up to now, behavioral interventions and pharmacological treatments show limited effectiveness, are costly or burdened with side effects. Brain stimulation techniques could represent an alternative to the current treatments. In particular, stimulation of the vagus nerve - the so-called gut-brain axis - is promising because it is a core component in the regulation of body weight and of eating behaviour. Indeed, evidence exists from animal models and from the treatment of patients with epilepsy or major depression, that stimulating the vagus nerve via implanted electrodes (VNS) has a profound impact on food consumption behavior, metabolism and body weight. However, in contrast to previous studies, the present investigation used a transcutaneous vagus nerve stimulation (tVNS) and tested its potential impact on the regulation of body weight.

In a pre-post study design, 34 healthy, male subjects with a Body Mass Index (BMI) ≥ 27 kg/m2 received either a tVNS or a sham stimulation at the left outer ear over 5 weeks. Despite body weight and body height, additionally metabolic (blood parameter, basal metabolic rate (BMR), body composure), neuronal (resting state-MRI, functional MRI) and behavioral parameters (wanting/liking, approach-avoidance tendencies) were collected enabling the investigation of interactions across systems.

Particularly, first results to its effects on the food approach-avoidance behaviour (AAT task), the neuronal activity and blood parameter are presented.

Finally, preliminary conclusions are drawn, and further planned analysis are outlined.

Poster Session

D3 - Body mass gain in Parkinson´s Disease following deep brain stimulation: A systematic meta-analysis and preliminary study data

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Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a well-established therapy in advanced Parkinson's disease (PD) for managing severe motor complications. However, a remarkable weight gain has been consistently reported after STN-DBS surgery, which - at least in part – counteracts the positive effects of motor improvement.
Methods: For this systematic review and meta-analysis, a computerized search for relevant articles was performed in MEDLINE, Cochrane Library, Clinical Trials, and Livivio against a priori inclusion/exclusion criteria. Main outcome parameters were body weight and body mass Index (BMI). Effect size was calculated by Cohens' d.
Results: 38 out of 154 studies were included in this meta-analysis with a total sample size of 979 patients and follow-up time between 1 and 60 months after surgery. Mean age across studies was 59.0±7.5 years. Over all studies, mean weight gain for the longest follow-up period in each study was 5.2 kg ($p<0.0001$) with corresponding effect size of $d=0.64$. For BMI, mean increase over all studies was 1.8 kg/m2 ($p<0.0001$; $d=0.78$). Prior to STN-DBS surgery, 40% of the patients were overweight. After surgery, this proportion increased up to 78%. Body weight increased continuously within the following time intervals: +2.9 kg ($d=0.69$) at 3 months, +3.9 kg ($d=0.216$) at 6 months, +6.4 kg ($d=0.72$) at 12 months, and +6.3 kg ($d=1.02$) at >12 months, respectively, after surgery.
Conclusion: In view of negative health implications of weight gain, the development of tailored therapies to prevent obesity and accompanied metabolic disorders after STN-DBS surgery is required.

Poster Session

E1 - Infrared thermography – a non-invasive method for the assessment of brown adipose tissue (BAT) in humans

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Especially newborns utilize brown adipose tissue (BAT) in order to keep their body temperature constant. Meanwhile, the presence of BAT has been recognized also in adult humans. The metabolic role of BAT has gained enormous scientific attention as a potential target in the treatment and prevention of obesity and metabolic disease. Currently, the gold standard for non-invasive detection of BAT activation in humans is 18F-fluorodeoxyglucose PET and computed tomography (18F-FDG PET-CT). However, PET-CT scan holds major limitations as e.g. high doses of ionizing radiation and high procedure cost. These limitations preclude the use of PET-CT to evaluate BAT on a routine base in clinical trials. There is a clear need for alternative imaging methods to study BAT activity in vivo.
Infrared thermography (IRT) is a promising method to detect and quantify BAT in humans. IRT implies the use of a thermo camera and is a 2-step methodology comprising imaging acquisition and imaging analysis. Recently, numerous advantages of IRT, including its safety, reliability and inexpensiveness compared to FDG PET-CT, have been suggested. Although widely employed to assess BAT in animal studies, the use of IRT for human studies remains scarce. With our project we aim to establish a standardized and reproducible protocol for thermographic imaging as non-invasive method to measure BAT activity in the supraclavicular area in humans.

Poster Session

E2 - Dopamine signalling in the control of thermogenic adipose tissue

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Brown adipose tissue (BAT) generates heat by combusting excess calories through „uncoupling protein 1" (Ucp1). This process, referred to as thermogenesis, highlights BAT as an important regulator of energy balance and potential target for treating diabetes. Thermogenesis is triggered by the hypothalamus in response to cold via the sympathetic nervous system, which releases catecholamine neurotransmitters on BAT. To date, the dopamine (DA) derivatives norepinephrine and epinephrine have been shown to be potent BAT-activating neurotransmitters. The molecular effects of DA on BAT thermogenesis however have yet to be elucidated. Recently, in vitro studies unveiled that D1- and D2-like dopamine receptors (DRD1, DRD2) are expressed in immortalized murine brown adipocytes and that DA increases mitochondrial thermogenesis via DRD1. Our in vivo data now show in mice that the DRD1 agonist SKF38393 (10 mg/kg; 7d; i.p.) significantly increased cAMP protein in BAT, but had no significant effect on BAT temperature as assessed by infrared thermography or Ucp1 mRNA expression. However, it significantly reduced white fat mass and hepatic glycogen content. The DRD2 agonist Sumanirole (3,2 mg/kg; 7d; i.p.) had no significant effect on BAT temperature, fat mass or cAMP levels, while it significantly reduced Ucp1 mRNA expression in BAT. Taken together our data reveal only minor effects of D1 and D2 agonists on BAT function in vivo, which will be compared in future experiments to the effects of DA itself.

Poster Session

E3 - Thyroid hormone induced browning of white adipose tissue does not contribute to thermogenesis

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Regulation of body temperature critically depends on thyroid hormone (TH). Recent studies revealed that TH activates brown fat thermogenesis and induces browning of white adipose tissue, possibly contributing to the observed hyperthermia in hyperthyroid patients and potentially providing favourable metabolic effects. In this study, we show that browning of white fat by TH requires TH receptor beta and likely occurs independently of the sympathetic nervous system, as it is still observed at thermoneutrality with minimal norepinephrine stimulation. Despite high levels of uncoupling protein 1 (UCP1), both, brown and beige fat of hyperthyroid mice are not metabolically active, as glucose and lipid uptake are decreased. Most importantly, the metabolic and thermogenic effects of the hormone were maintained in hyperthyroid UCP1-knockout mice, demonstrating that they do not require brown or beige fat, respectively. Skeletal muscle of hyperthyroid mice showed decreased glycogen content, as well as increased lipid uptake, indicating an increased metabolic rate, possibly contributing to the observed hyperthermia. Our findings clarify the mechanisms contributing to hyperthermia in systemic hyperthyroidism and underline that the mere presence of UCP1 is insufficient to draw conclusions on its activity and the therapeutic potential of a browning agent. The authors declare no conflict of interest.

Poster Session

E4 - Cerebral endothelial dysfunction alters metabolism and worsens hypercapnia-induced body temperature changes in mice

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More than 40% of obese patients develop obstructive sleep apnea and endothelial dysfunction as a secondary symptom. Obstructive sleep apnea is associated with hypercapnia. In endothelial dysfunction vessels fail to respond to stimuli (e.g. CO2) that normally trigger vasodilation or vasoconstriction. How the pathological changes, obstructive sleep apnea and endothelial dysfunction, affect each other or the underlying metabolic changes, is unknown so far. Our study addresses the question, whether cerebral endothelial dysfunction itself or together with hypercapnia alters metabolism and might promote pathological changes. For that purpose we use a Gαq/11 brain endothelial knockout (Gαq/11beKO) mouse model to mimic cerebral endothelial dysfunction. We observed a 12.5% reduction in energy expenditure and a 28.6% increase in body fat in Gαq/11beKO mice in comparison to controls. To model hypercapnia, we exposed Gαq/11beKO and control mice to elevated CO2 levels (10%) in the ambient atmosphere for a short period (10 minutes). Using thermography, upon CO2 exposure we observed a dramatic decrease of brown adipose tissue temperature in Gαq/11beKO mice compared to controls, revealing differences in body temperature regulation. The body temperature itself decreased only in Gαq/11beKO mice but not in controls. The data show that cerebral endothelial dysfunction itself has an effect on the metabolism and that together with hypercapnia, dramatic changes in body temperature occur. We speculate that the hypothalamus, as a central regulatory region of body temperature and metabolism, plays an important role in the altered regulation and that this effect is mediated by the brown adipose tissue.

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