PROGRAM AND ABSTRACTS

4th International Meeting on Physiology and Pharmacology of Temperature Regulation

Hotel Resort Ferradura
Búzios, RJ
March 22-25, 2012
Sponsors & Support
Welcome Letter

Dear Colleagues,

Welcome to Búzios! Your participation in the 4th International Symposium on Physiology and Pharmacology of Temperature Regulation 2012 (PPTR2012) is a great pleasure and honor to us! The goal of the symposium is to make you return home enthusiastically motivated with an improved understanding of temperature regulation from molecular, biochemistry, physiology (including comparative physiology) and pharmacology through clinical management. As happened in the last years, a special happening of this meeting is the Young researches awards presentation in which the young scientists were encouraged to participate and compete. We hope that you enjoy your stay in Búzios and do not lose the occasion to get to know the outstanding beauty of Búzios, a city full of charm and beauty!

With our best wishes for a pleasant scientific and social meeting,

Glória E. P. de Souza               Maria Camila Almeida
Local Organizing Committee

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Nigel Taylor (Australia)
Quentin Pittman (Canada)
Stephen Kent (Australia)
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22 March 2012 (Thursday)

14h00
Venue Secretariat Opening

18h30
Opening Session
Ruediger Gerstberger (University of Giessen, Germany) / Glória E. P. Souza (USP)

19h00
Conference 1
Multidimensional phenotype of individual WS Neurons of the mouse POA
Jim Eberwine (University of Pennsylvania, USA)

23 March 2012 (Friday)

08h00-09h15
Symposium 1
Epigenetic mechanisms in the establishment of thermal adaptation/thermotolerance
Chairperson: Michal Horowitz (The Hebrew University, Israel)
- Epigenetic regulation of thermotolerance acquisition during the critical period of sensory development
  Noam Meiri (The Volcani Center, Israel)
- Within life’ heat acclimation mediated cytoprotective memory: Does epigenetic mechanisms play a role
  Michal Horowitz (The Hebrew University, Israel)
- MicroRNAs and Metabolic Depression: Reorganizing while shutting down the fires of life or mammalian hibernation: MicroRNAs take Center Stage
  Kenneth Storey (Carleton University-Canada)
- Single cell transcriptomics and control of cellular phenotype
  Jim Eberwine (University of Pennsylvania, USA)

09h15-09h45 Coffee-Break

09h45-10h30
Symposium 2
Rhythmicity of body temperature – Hourly, Daily, and Seasonal
Chairperson: Roberto Refinetti (University of South Carolina, USA)
- Hourly Rhythmicity
  Roberto Refinetti (University of South Carolina, USA)
- Daily Rhythmicity: Field Studies
  Shane Maloney (University of Western Australia, Australia)

10h30-11h30
Lecture 1
Skin temperature, sleep and vigilance
Eus W. Van Someren (VU University, Netherlands)

11:30-14h00 Lunch

14h00-15h30
Symposium 3
Mechanisms and controllers of heat loss responses during heat stress in humans
Chairperson: Glen Kenny (University of Ottawa, Canada)
- The distributions of thermal and emotional sweating: challenging some persistent teachings
  Nigel Taylor (University of Wollongong, Australia)
- Heat dissipation in grafted skin
  Craig Crandall (University of Texas Southwestern, USA)
- Altered local mechanisms of cutaneous vasodilatation and vasoconstrictor in essential hypertension
  Lacy A Holowatz (Penn State, USA)
- Is the body’s ability to dissipate heat compromised following exercise-induced heat stress?
  Glen Kenny (University of Ottawa, Canada)

15h30-16h45
Lecture 2
Body temperature daily rhythms in diurnal and nocturnal rodents – the response to illumination manipulations
Abraham Haim (University of Haifa, Israel)

16:45-17:45
Symposium 4
Mechanisms of thermal pleasantness - from basic to applied
Chairpersons: Kei Nagashima (Waseda University, Japan / Andrej A. Romanovsky (St. Joseph's Hospital, USA)
- Mapping a group of hypothalamic neurons that mediates cold-seeking behavior in endotoxin shock
  Samuel P. Wanner (UFMG)
- Locomotor activity as a thermoeffector: role of TRPV1
  Andrej A. Romanovsky (St. Joseph’s Hospital, USA)
- Mice modulates behavioral thermoregulation in heat during plasma hyperosmolality and the influence of daily activity
  Kei Nagashima (Waseda University, Japan)
- Thermal perception in heat is modulated by plasma hyperosmolality; comparison between trained and non-trained young men
  Ken Tokizawa (Waseda University, Japan)
17h45-18h45
Lecture 3
New developments in metabolic measurement and behavioral analysis.
John R. Lighton (President Sable Systems International)

18h45-19h45
Poster Session
• PT.01-PT.30

24 March 2012 (Saturday)

8h30-09h45
Symposium 5
The cannabinoid-1 (CB1) receptor: at the crossroads of thermoregulation and systemic inflammation
Chairpersons: Andrej A. Romanovsky (St. Joseph's Hospital, USA) / Glória E. P. de Souza (USP)
• Contributions of CB1 receptors to fever: unexpected findings from the CB1 knockout.
  Quentin J. Pittman (University of Calgary, Canada)
• Anandamide-induced fever is dependent on prostaglandins, opioids, and interleukin-1
  Daniel Fraga (UFPR)
• Central CB1 receptors mediate initiation of hypotension during septic shock
  Carlos Feleder (Albany College of Pharmacy, USA)
• Lipopolysaccharide-induced hypothermia critically depends on brain CB1 receptors.
  Alexandre A. Steiner (Albany College of Pharmacy, USA)

09h45-10h15 Coffee Break

10h15-11h30
Symposium 6
Fever mediators and antipyretics
Chairperson: Joachim Roth (University of Giessen, Germany) / Duncan Mitchell (University of the Witwatersrand, South Africa)
• The putative JAK-STAT inhibitor AG490 and the putative NFkB inhibitor parthenolide show differential effects on fever and brain inflammatory markers during LPS-induced systemic inflammation in rats.
  Christoph Rummel (University of Giessen, Germany).
• Role of chemokines and its receptors on the CNS for inducing fever response.
  Denis de Melo Soares (UFBA)
• Peripherally-released IL-10 and immune to brain signaling in mediating fever.
  Lois Harden (University of Witwatersrand, South Africa)
• Antipyretic effect of dipyrone metabolites on fever induced by LPS and Tityus serrulatus venom (Tsv)
  David do Carmo Malvar (USP).

11:30-13h30 Lunch

13h30-15h00
Poster Session
• PT.31-PT.61

15h00-17h00
Symposium 7
Interactions between metabolism and fever: adding fuel to the fire!
Chairpersons: Giamal N. Luheishi (McGill University, Canada) / Stephen Kent (LaTrobe University, Australia)
• Molecules regulating temperature in response to calorie intake
  Bruno Conti (Scripps Institute, USA)
• Early inflammation: programming adult innate and metabolic pathways
  Quentin J. Pittman (University of Calgary, Canada)
• Metabolic signals & the fever-hypothermia dichotomy in systemic inflammation
  Alexandre A. Steiner (Albany College of Pharmacy and Health Science, USA)
• The effects of diet induced obesity on the febrile response to LPS
  Giamal N. Luheishi (McGill University, Canada)
• Calorie restriction attenuates LPS-induced sickness fever
  Stephen Kent (LaTrobe University, Australia)

17h00-18h00
Conference 2
Brain Temperature: Regulation or Homeostasis?
Eugene A. Kiyatkin (NIH, USA)

25 March 2012 (Sunday)

08h30-10h30
Symposium 08
Brown fat: cross-fertilization between animal and human studies
Chairpersons: Wouter van Marken Lichtenbelt (Maastricht University, The Netherlands) / Jan Nedergaard (Stockholm University, Sweden)
• Brown adipose tissue activity and triglyceride clearance
  Jan Nedergaard (Stockholm University, Sweden)
• Implications of the thermoneutral zone in human BAT studies
  Boris Kingma (Maastricht University, The Netherlands)
• Sympathetic and sensory innervation of brown adipose tissue
  Timothy Bartness (Georgia State University, USA)
• Brown fat activation by cold and insulin
  Kirsi Virtanen (Turku PET Center, Finland)
• Low environmental temperature and obesity
  Wouter van Marken Lichtenbelt (Maastricht University, The Netherlands)

10h30-11h00 Coffee Break
11:00-12:30
Symposium 9
Therapeutic Cranial Cooling and Natural Selective Brain Cooling in Humans
Chairperson: Matthew D. White (Simon Fraser University, EUA)
- Cerebral heat balance and oxygenation during exercise with hyperthermia
  Lars Nybo (University of Copenhagen, Denmark)
- Effects of active and passive heat stress on mechanisms modulating cerebral perfusion
  Craig Crandall (University of Texas Southwestern Medical Center, USA)
- Human Selective Brain Cooling and Pulmonary Ventilation
  Matthew D. White (Simon Fraser University, Canada)

12h30-14h00 Lunch

14h00-16h00
Symposium 10
Young researches awards presentation
Chairperson: Ruediger Gerstberger (University of Giessen, Germany)

16h00-16h30 Coffee break

16:30-17:45
Closing Conference
TRP channels in thermoregulation
Andrej A. Romanovsky (St. Joseph’s Hospital, USA)

17h45-18h15
Awards Announcement & Closing Words
Chairperson: Ruediger Gerstberger (University of Giessen, Germany)
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<td><strong>PT.05</strong> Hydrogen sulfide as a cryogenic mediator of hypoxia-induced anapnoxia. Kwiatkoski M, Soriano RN, Branco LGS – FMRP-USP – Fisiologia, FERP-USP – Fisiologia, FERP-USP – Fisiologia</td>
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<td><strong>PT.06</strong> Expression of thermosensitive TRP ion channel genes in hypothalamus of normal and cold adapted rats. Voronova IP, Tuzhikova AA, Kozyreva TV Russian Academy of Medical Sciences – Physiology – Thermophysiology</td>
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<td><strong>PT.09</strong> Influence of il6st gene on thermoregulation and blood level of Interleukine-6. Khramova GM, Voronova IP, Kulikov AV, Kozyreva TV – Russian Academy of Medical Sciences – Physiology – Thermophysiology, Russian Academy of Sciences – Cytology and Genetics – Neurogenomic of Behavior</td>
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<td><strong>PT.11</strong> Meth-induced hyperthermia is a multi-phase phenomenon resulting from serial and overlapping actions on different anatomical sites. Sanchez-Alavez M, Conti B, Zhurkov V, Wood M, Fox HS, Bartfai T, Marcondes MC – The Scripps Research Institute – Molecular and Integrative Neurosciences, University of Nebraska Medical Center – Pharmacology and Experimental Neurosciences</td>
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<td><strong>PT.12</strong> Heat acclimation increases hypoxia-inducible factor 1 alpha expression but not erythropoietin and vascular endothelial growth factor in athletes. Shin YO, Kim TW, Han MK, Lee JB, Min YK, Yang HM – Soonchunhyang University – Health Care, Graduate School, Soonchunhyang University – Physiology</td>
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<td><strong>PT.13</strong> Absence of non-shivering thermogenesis in older people during mild cold exposure: possible role of arrhenius law? Kingma BRM, van Marken Lichtenbelt WD NUTRIM-Maastricht University Medical Center – Human Biology</td>
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<td><strong>PT.15</strong> Activation of (non-)nitrergic hypothalamic MnPO neurons due to systemic thermal and osmoregulatory stimulations in the rat. Gerstberger R, Ott D, Marks D, Weber T, Roth J Justus-Liebig-University Giessen – Veterinary Physiology and Biochemistry</td>
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<td><strong>PT.16</strong> Age-dependent decline of hypothalamic neurogenesis and of heat tolerance in long-term heat-acclimated rats. Matsuzaki K, Katakura M, Hara T, Hashimoto M, Shido O Shimane University – Medicine</td>
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| **PT.18** Assessing vasomotor dysfunction to investigate peripheral neuropathy. Wu Y, Nieuwenhoff MD, Huynen FJPM, Van der Helm FCT, Niehof S, Schouten AC – Delft University of Technology –
Biomechanical Engineering, 2Erasmus Medical Center – Anesthesiology

PT.19
Social defeat stress-induced hyperthermia involves brown adipose tissue thermogenesis mediated by medullary raphe sympathetic premotor neurons. Nakamura K1, Lkhagvasuren B2, Kataoka N1, Nakamura Y1, Oka T3 - 1Kyoto University – Career-Path Promotion Unit for Young Life Scientists, 2Kyushu University – Psychosomatic Medicine

PT.20
Comparative thermoregulatory physiology and behavior of blue and black wildebeest. Lease HM, van Staden A, Fuller A, Hetem RS University of the Witwatersrand – Physiology

PT.21
Adaptive modification of hormones related with thermoregulation after short-term heat acclimation in athletes Shin YO1, Kim TW2, Lee JB3 1Soochunhyang University – Health Care, Graduate School, 2Soochunhyang University – Health Care, 3Soochunhyang University – Physiology

PT.22
Limb regeneration stabilizes thermoregulatory preference in the red-spotted newt (Notopthalmus viridescens). Tattersall GJ, Tyson TM, Lenchshyn JR, Car lone RL Brock University – Biological Sciences

PT.23
Endogenous hydrogen sulfide mediates LPS-induced fever in rats. Kwiatkoski M1, Araújo R2, Azevedo L2, Carnio EC3, Soriano RN3, Branco LGS2 - 1FMRP-USP – Fisiologia, 2FORP-USP – Morfologia, Estomatologia e Fisiologia, 3USP – Enfermagem Geral e Especializada

PT.24
Inhibition of peripheral hydrogen sulfide synthesis modulates endotoxic fever. Soriano RN1, Cunha JS1, Batalhão ME1, Kwiatkowski M2, Branco LGS3, Carnio EC1, Soriano RN2, Branco LGS2 - 1FMRP-USP – Fisiologia, 2FORP-USP – Morfologia, Estomatologia e Fisiologia,

PT.25
Intracerebroventricular administration of leptin increase physical activity but has no effect on metabolism in cold-acclimated rats. Tang GB, Wang DH Chinese Academy of Sciences – Zoology – Integrated Management of Pest Insects and Rodents

PT.26
Contribution of the dopamine receptor 1 (D1R) within the paraventricular nucleus in the heat stress-induced cardiovascular and thermoregulatory adjustments. Guimarães JB1, Leite LHR2, Zheng, H1, Coimbra CC1, Patel KP3 1UFMG – Fisiologia e Biofísica, 2UFJF – Fisiologia, 3University of Nebraska Medical Center – Cellular and Integrative Physiology, 4University of Nebraska Medical Center – Physiology

PT.28
Daily wheel running in mild heat improves heat tolerance and acclimation in mice: its relation to hypothalamic mechanisms. Tokizawa K Waseda University – Sport Sciences

PT.29
Activation of hemostatic pathways by exercise induced hyperthermia. Eijsvogels TM1, Veltmeijer, MT1, van Geffen, M2, Thijssen, DH1, van Heerde, WL2, Hopman, MT1 - 1Radboud University Nijmegen Medical Centre – Physiology, 2Radboud University Nijmegen Medical Centre – Heamatology

PT.30
Effect of hypoxic training on exercise thermoregulatory responses. Kounalakis SN1, Eiken O2, Mekjavic IB3 1Evelpidon Hellenic Military University – Human Performance-Rehabilitation Laboratory – Physical and Cultural Education, 2Royal Institute of Technology – Environmental Physiology, 3Jozef Stefan Institute – Automation, Biocybernetics and Robotics

PT.31
Heat-Intolerance earlier identification using molecular marker in lymphocytes. Horowitz M1, Kopeliovich D2, Mekjavic IB3 1Evelpidon Hellenic Military University – Human Performance-Rehabilitation Laboratory – Physical and Cultural Education, 2Royal Institute of Technology – Environmental Physiology, 3Jozef Stefan Institute – Automation, Biocybernetics and Robotics

PT.32
Chronic absence of tail artery innervation impairs cutaneous heat loss during physical exercise in thermoneutral and warm environments. Lima MRM1, WBand SP2, Coimbra CC2, Lima NRV1 1UFMG – Educação Física, 2UFMG – Fisiologia e Biofísica

PT.33
Effects of chronic absence of arterial baroreceptors on exercise performance in the heat. WBand SP1, Fonseca, I.A.T1, Vaz GF2, Fumega U2, Coimbra CC2, Lima NRV1 1UFMG – Educação Física, 2UFMG – Fisiologia e Biofísica

PT.34
Exercise intensity affects the rate of increase of frontal cortex temperature, but does not change the absolute value at the voluntary interruption of the effort. Kunstetter AC1, Wilke CF1, Madeira LG1, Lima MRM2, Wanner SP2, Rodrigues LOC1, Lima NRV1 1UFMG – Fisiologia do Exercício, 2UFMG – Educação Física

PT.35
Running exercise with and without a ventromedial hypothalamic thermal clamp. Fonseca CG, Wanner
PT.36

PT.37
Neuronal basis for the hypothermic effect of antiepileptic drugs with GABAergic mechanisms of action. Yakimova KS Medical University of Sofia – Pharmacology & Toxicology

PT.38
Coping with systemic inflammation and sepsis: value of the fever-hypothermia switch. Steiner AA1, Liu E1, Lewis K1, Al-Saffar H1, Krall CM1, Corrigan JJ1, Singh A2, Musteata ML1, Bakshi CS1, Romanovsky AA2, Sellati TJ1 1Albany College of Pharmacy and Health Sciences – Pharmaceutical Sciences, 2Albany Medical College – Immunology and Microbial Disease, 3New York Medical College – Microbiology and Immunology, 4St Josephs Hospital and Medical Center – Systemic Inflammation laboratory

PT.39
Permanent changes in thermoregulation and cardiovascular response to cold stress in offspring of rats exposed developmentally to endocrine disruptors. Gordon CJ1, Johnstone A1, Grace C1, Aydin C2, Rogers JM1, Gilbert ME1 – 1US EPA – Toxicity Assessment, 2University of Uludag – Physiology

PT.40
Interstitial calcium concentration modulates human eccrine sweating. Metzler-Wilson K1, Sammons D2, Wilson TE3 1Lebanon Valley College – Physical Therapy, 2HCOM-Ohio University – Specialty Medicine, 3HCOM-Ohio University – Biomedical Sciences

PT.41
L-arginine supplementation attenuates the increase in intestinal permeability and bacterial translocation induced by prolonged physical exercise in the heat. Costa KA1, Soares ADN1, Santos RGC1, Wanner SP2, Fernandes SOA3, Coimbra CC2, Cardoso VN4 1UFMG – Alimentos, 2ICB-UFMG – Fisiologia e Biofísica, 3UFMG – Análises Clínicas e Toxicológicas

PT.42
Pretreatment with glutamine blocks the increase in intestinal permeability and bacterial translocation induced by passive hyperthermia. Wanner SP1, Soares ADN2, Costa KA2, Santos RGC2, Fernandes SOA3, Coimbra CC2, Cardoso VN4 1UFMG – Fisiologia e Biofísica, 2UFMG – Alimentos

PT.43
Interleukin (IL)-6 and Endothelin-1 (ET-1) may not be involved on Poli I:C fever. Bastos-Pereira AL, Fraga D, Zampronio AR UFPR – Farmacologia

PT.44
Previous freezing cold injury does not affect temperature-induced digit vascular responses. Mekjavic, IB1, Gorjanc J2, McDonnell AC3, Mičinski, M4, Eiken, O5, Morrison SA6 1Jozef Stefan Institute – Automation, Biocybernetics and Robotics, 2Hospital of the Brothers of St. John of God, 3Jozef Stefan International Postgraduate School, 4University Medical Centre – Nuclear Medicine, 5Royal Institute of Technology – Environmental Physiology, School of Technology and Health, 6Jozef Stefan Institute – Automation, Biocybernetics and Robotics

PT.45
Effects of the PPAR-γ agonist Rosiglitazone on LPS-induced systemic inflammation and on mitochondrial biogenesis in old and young rats. Koenig S1, Wenz T2, Gerstberger R1, Roth J1, Rummel C1 1Justus-Liebig-University Giessen, Germany –Veterinary Physiology and Biochemistry, 2University of Cologne – Genetics

PT.46
CCL3/MIP1α induces calcium signaling in cells from rat pre-optic area microcultures but not TNF-α or IL-6 synthesis. Soares DM1, Ott D2, Souza GEP3, Roth J2 1FCFRP-USP – Pharmacology/ UFBA – Pharmacy, 2Justus-Liebig-University Giessen, Germany –Veterinary Physiology and Biochemistry, 3FCFRP-USP – Pharmacology

PT.47
Hypothermia following exertional heatstroke treatment-three case reports. Moran DS1, Makrantz C2, Shapiro Y1, Helod Y2 1Ariel University Center of Samaria, 2Heller Institute – Sheba Medical Center

PT.48
Modification of central sudomotor mechanism and sweat gland function induced by long-term tennis training in relative active heat loading. Kim TW1, Shin YO1, Lee JB1, Min YK2, Yang HM2 1Soochunhyang University – Health Care, 2Soochunhyang University – Physiology

PT.49
Regulation of body temperature by free-living vervet monkeys (Chlorocebusaethiops). Fuller A1, Rabe K1, Mistry A1, Barrett L2, Henzi P2, Meyer L1, Mitchell D1, Helon R2 1University of the Witwatersrand – Physiology, 2University of Lethbridge – Psychology

PT.50
Development of behavioral thermoregulation model for evaluation of outdoor thermal environment. Kurazumi Y1, Tsuchikawa T2, Fukagawa K3, Yamato Y4
PT.51 Partial removal of brown adipose tissue enhances humoral immunity in warm-acclimated Mongolian gerbils (*Meriones unguiculatus*). Yang D, Xu Y, Wang DH State Key Laboratory of Integrated Management of Pest Insects and Rodents – Zoology, Chinese Academy of Sciences

PT.52 Habituation of thermal sensation, but not in thermoregulation, following repeated daily exposure to menthol in humans. Gillis DJ, Weston N, House JR, Tipton MJ Portsmouth University – Extreme Environments – Sport & Exercise Science

PT.53 Selective brain cooling as a water conservation mechanism in artiodactyls, Strauss WM1, Hetem, R1, Maloney SK2, Mitchell D1, Meyer L1, Fuller A1 – 1University of the Witwatersrand – Physiology, 2University of Western Australia – Physiology: Biomedical, Biomolecular, and Chemical Science

PT.54 Seasonal variation of core temperature and sweat rate in obese subjects. Sato M, Kanikowska D, Iwase S, Shimizu Y, Nishimura N, Inukai Y, Sugenoya J Aichi Medical University – Physiology


PT.56 Thermoregulation of free-living cheetah, *Acinonyx jubatus*. Hetem RS1, de Witt B1, Fick LG1, Meyer, L1, Maloney SK1, Mitchell, D1, Fuller A1 – 1University of the Witwatersrand – Physiology, 2University of Western Australia – Physiology: Biomedical, Biomolecular, and Chemical Science

PT.57 Finger and toe temperature responses to cooling and warming in elite alpinists with and without previous freezing cold injury. Morrison SA1, Gorjanc J2, McDonnell AC2, Milčinski, M1, Eiken, O1, Mekjavic, IB1 – 1Jozef Stefan Institute – Automation, Biocybernetics and Robotics, 2Hospital of the Brothers of St. John of God Jozef Stefan International Postgraduate School, 3University Medical Centre, 4Royal Institute of Technology – Environmental Physiology, School of Technology and Health

PT.58 Low environmental temperature and obesity. Van Marken Lichtenbelt WD NUTRIM School for Nutrition, Toxicology and Metabolism of Maastricht University Medical Center – Human Biology

PT.59 Acclimation to heat – evident from a Poincaré Plot analysis of heart rate variability. Epstein Y1, Heled Y1, R Kobo2, Levitan J2, Ketko I1, Moran DS3 – 1Sheba Medical Center – Heller Institute of Medical Research, 2Ariel University Center – Physics, 3Ariel University Center – Medical Sciences

PT.60 Do older adults store more heat during work in the heat?: A calorimetric perspective. Kenny GP, Larose J University of Ottawa – Human Kinetics

PT.61 Effect of hypoxia and bedrest on peripheral vasoconstriction and sleep quality. McDonnell A C1, DolencGroselj L2, Jaki Mekjavic P3, Eiken, O4, Mekjavic, IB5, 1Jozef Stefan Institute – Automation, Biocybernetics and Robotics, 2University Clinical Centre Ljubljana – Clinical Neurophysiology 3University Clinical Centre – Eye Clinic 4Royal Institute of Technology – Environmental Physiology – Technology and Health, 5Jozef Stefan Institute – Automation, Biocybernetics and Robotics
Conferences

CF.2

Brain temperature: regulation or homeostasis? Kiyatkin EA NIDA. Intramural Research Program Behavioral Neuroscience Branch.

An organism’s internal temperatures remain relatively stable following robust fluctuations in environmental temperatures. This stability of internal temperatures is provided by the CNS via adjustment of metabolic activity and heat loss to the external environment. While the concept of regulation adequately explains body temperature fluctuations during environmental challenges, it apparently fails to explain temperature fluctuations in the brain, which depend upon its own metabolic activity and heat loss to or inflow from the body via cerebral circulation. In this report we present data on fluctuations in brain temperature occurring at stable environmental temperatures under physiological and behavioral conditions and discuss their mechanisms. Since most processes governing neural activity are temperature-dependent, we consider how naturally occurring temperature fluctuations could affect neural activity and neural functions. Then, we review brain temperature changes induced by drugs that affect brain metabolism and heat loss, with a focus on psychomotor stimulants, which are able to induce robust hyperthermia. Since high temperature could irreversibly damage neural cells and dramatically worsen various pathological processes, we consider the situations associated with pathological brain hyperthermia and evaluate its role of in acute perturbations of brain functions, neurotoxicity and neurodegeneration. We also focus on complexities and limitations in consideration of brain temperature within the frameworks of physiological regulation and homeostasis. While different adaptive mechanisms could, within some limits, compensate for an altered heat balance of the brain, real life often creates the situations when this balance could not be compensated, resulting in pathology and acute life-threatening health complications.

Lectures

LT.1

Skin temperature, sleep and vigilance. Van Someren EJW Netherlands Institute for Neuroscience - Sleep & Cognitions.

Brain areas involved in sleep and biological rhythm regulation are sensitive to light and temperature, which in an evolutionary sense are the oldest cyclically varying physical aspects of the environment. We have therefore proposed that the 24-cycle of sleep and wakefulness is likely to show a thermosensitivity that is firmly rooted at the systems level of the responsible network of brain areas including the preoptic area and anterior hypothalamus (1-3). In contrast to previous work by other groups, we reasoned that skin temperature rather than the previously proposed local brain temperature would be of major importance. We have built a dedicated experimental setup that allows for clamping of skin temperature while measuring brain activity and performance in humans. With the use of this setup we were able to confirm our hypothesis by showing that the induction of minute changes in skin temperature within the thermoneutral and comfortable range had pronounced effects on sleep and vigilance in healthy young and elderly people as well as in the sleep disorders of insomnia and narcolepsy (4-10). These studies concurrently provide the first and ample evidence for a causal role of skin temperature in vigilance state modification and call for applications to optimize e.g. bed-temperature for sleep and the temperature of chairpersons during work for vigilance. A recent ensuing second line of research focuses on the spontaneous fluctuations in skin temperature within the comfortable range: our hypothesis would predict these to be informative for fluctuations in sleep depth and vigilance level. Indeed we just obtained data confirming that skin temperature measurements are of value in the detection of sleepiness and lapses of attention – a major cause of traffic and control accidents – during the day (11). Likewise, skin temperature measurements are of value in the detection of sleep versus immobile wakefulness during the night, yielding an essential possibility to improve ambulatory sleep monitoring devices like actigraphs. Finally, we addressed possible abnormalities in skin temperature and its association with sleep and vigilance in people with sleep disorders. In narcolepsy, we thus demonstrated a deficiency in the skin vasoconstriction response to attaining an upright posture (12). The consequent elevated skin temperature during wakefulness seems involved in the problems these patients have with staying awake. In a voxel-based morphometry (VBM) MRI study in a more common sleep disorder, insomnia, we found a decrease in gray matter volume in the orbitofrontal cortex, on spot in a key area for the evaluation of thermal comfort (13). Moreover, the less gray matter in this area, the more severe the sleep complaints were. Indeed, we confirmed deficits in the subjective evaluation of thermal comfort in insomnia patients (8). Concertedly, our studies indicate a close link between thermoregulation and vigilance regulation, and provide new avenues for the development of treatments for disorders of sleep and alertness. 1. Van Someren EJW (2000) ChronobiolInt 17:313-354; 2. Van Someren EJW (2003) Sleep and Biological Rhythms 1:55-64; 3. van Someren EJW (2006) Prog Brain Res 153:309-324; 4. Raymann RJEM et al (2005) Am J Physiol 288:R1589-R1597; 5. Raymann RJEM and Van Someren EJW (2007) Sleep 30:96-103; 6. Raymann RJEM et al (2007) Physiol Behav 90:257-266; 7. Raymann RJEM et al (2008) Brain 131:500-513; 8. Raymann RJEM and Van Someren EJW (2008) Sleep 31:1301-1309; 9. Fronczek R et al (2008) Sleep 31:233-240; 10. Fronczek R et al (2008) J Neurol Neurosurg Psychiatry 79:1354-1357; 11. Romeijn N and Van Someren EJW (2011) J Biol Rhythms 26:68-
and furthermore, to study the T_b daily rhythm response

N1, Kisliouk T1, Yossifoff M1, Cramer T1 - ARO, The:

Epigenetic regulation

SP1

Symposia

LT.2

Body temperature daily rhythms in diurnal and nocturnal rodents – the response toillumination manipulations. Haim A. University of Haifa – Biology.

Background: One marked difference between nocturnal and diurnal species is the fact that in nocturnal species both, the raise in T_b and in melatonin (MLT) secretion takes place during the dark period of the 24h cycle. However, diurnal species split them, where maximal T_b values are during the light-phase and those of MLT are at the dark-phase. Light interference was found to effect T_b daily rhythms, what about dark interference (DI) at day time?

Aims: To study the response of T_b daily rhythms to DI in a nocturnal (Merionesstristrami) and diurnal species (Psammomysobesus) of the same family (Gerbillidiae) and furthermore, to study the T_b daily rhythm response in manipulating food intake to nighttime of P. obesus.

Results: Our results show that DI of 2h to the diurnal species abolished T_b daily rhythms while such a treatment to the nocturnal species resulted in T_b values increase, but the treated individuals kept a T_b daily rhythm similar to that of the control group. Furthermore, changing the feeding timing of P. obesus to dark-phase resulted with a similar response as to DI and the tested individuals lost their T_b daily rhythms.

Conclusions: The differences between the two species may support the idea for finding a diurnal animal model species, for drawing conclusions on human thermoregulation, as in our case P. obesus that become a-rhythmic. From our initial results it is suggested that for the diurnal species P. obesus the default is becoming a-rhythmic. The question to be asked: is this also the case in humans?

Symposia

SP1.1

Epigenetic regulation: early life environmental experiences affect thermoregulation development. Meiri N1, Kisliouk T1, Yossifoff M1, Cramer T1 - ARO, The Volcani Center. Institute of Animal Science.

Thermoregulation acquisition involves neuronal network remodeling and hence, alteration in the repertoire of expressed proteins. Here we describe epigenetic changes associated with thermal-control establishment in chicks.

We demonstrate increase of histone H3 di-methylation at lysine 27 during thermal-control establishment at the initiation of the BDNF coding region. Furthermore, antisense “knockdown” of the H3K27-specific methyltransferase, EZH2, which was induced in correlation with the methylation of H3K27, disrupted the thermal set-point and inhibited Bdnf mRNA expression. In a second stage of epigenetic regulation of thermal control establishment we demonstrate, during heat conditioning (day 3 posthatch), reduction of CpG methylation at the promoter area of BDNF in a CREB binding site accompanied by an increase of CREB binding to the DNA.

In a third level of gene expression regulation, we demonstrate the inhibitory role of microRNAs (miRNAs) in regulation of EZH2 expression in thermoregulatory systems. During heat conditioning at the critical period of thermal control establishment, there was a decrease in the expression of the EZH2-targeting miR-138 simultaneously with an increase in EZH2 levels in the preoptic anterior hypothalamus (PO/AH). Intracranial injection of miR-138 led to transient reduction of EZH2, which was also accompanied by a decrease in H3K27 methylation. Injection of miR-138 followed by heat conditioning abolished EZH2 induction, which is known to be significantly elevated during heat conditioning. Moreover, this miR-138-induced inhibition of EZH2 during the critical period resulted in a long-term effect on EZH2 expression. Finally, miR-138 injection during the critical period disrupted the establishment of thermoregulation, which was manifested in defective body temperature response to heat.

These data demonstrate a multilevel regulation mechanism of thermal control establishment, which includes both epigenetic and miRNA regulatory mechanisms.

Sponsored by: BARD, ISF, The chief scientist of the Israeli ministry of agriculture.

SP1.2

‘Within life’ heat acclimation induced memory: Does epigenetic mechanisms contribute? Horowitz M, Tetievsky A The Hebrew University - Laboratory of Environmental Physiology.

Heat-acclimation (AC) is “within lifetime” phenotypicadaptation to long-term elevations in ambient temperatures. The underlying mechanisms of AC include a continuum of genomic responses that reprogram gene expression to enlarge cytoprotective protein reserves, and in turn, to improve endurance in temperature extremes. AC also reinforces/interferes with the ability to combat novel stressors. The basis of this phenomenon relies on shared utilization of (or competition for) cytoprotective mechanisms. Activation of subsets of differentially expressed genes, unique to each stimulus or to each tissue/organ, ultimately determines the specific protective phenotype. The benefits of acclimation decay with time; reacquisition of the acclimation is faster than the time required to acclimate initially. Studying in tandem physiological and global genomic responses in rat, confirmed a dichotomy between molecular and physiological events during the loss of acclimation, suggesting that AC induces a long-lasting transcriptional program, enabling rapid re-acclimation via epigenetic transfer of information, predisposing to cellular cytoprotective memory. Postranslational histone tail modifications (histones H3 and H4) leading to an active chromatin state in the heat shock element (HSE) of the hsp70 and hsp90 genes throughout AC, acclimation-decay and ReAC regimen were associated with: i) a constitutive binding of HSF-1 to the hsp70 promoter and greater HSP-70 reserves at comfort temperatures and ii) a rapid resumption of the acclimated cytoprotected phenotype, when re-exposure to acclimation conditions replenished HSP90 stores. Phosphorylated MSK1/2
binding to the promoters of hsp70 and hsp90 appears to be upstream to these modifications. The dependency of the modifications involved on ambient temperature are discussed.

### SP1.3

**Multidimensional Phenotype of Individual WS Neurons of the Mouse POA.**

Eberwine Jim¹, Spaethling J¹, Buckley², Bartfai T² - ¹Department of Pharmacology, Perelman School of Medicine - PENN Genome Frontiers Institute, University of Pennsylvania, ²The Scripps Research Institute - Molecular and Integrative Neurosciences

Understanding of the phenotype from any particular cell type including its function requires precise quantitative measurements of its composite cell biology. In thinking about functional phenotype of warm sensitive neurons we decided that to understand the physiological potential of these cells that we wanted to know what all possible proteins could be expressed in these cells are including the druggable proteins, such as GPCRs and ion channels. To accomplish this we performed single cell transcriptomics (microarrays and NextGen sequencing) on individual electrophysiologically characterized warm sensitive neurons isolated from the live slice preparation of the mouse. While the presence of mRNA does not necessarily mean that the protein is present it does show the potential of the cells to express that protein. Intriguingly there are several hundred GPCR encoding mRNAs in individual WS neurons. We have gone on to assess (using pharmacological and knock-out strategies) whether or not these mRNA encode functional receptors in these neurons and have shown >10 of these receptors are functional on these cells. The functionality of some of these receptors suggests a connection between different physiological systems such as the functionality of the insulin receptor on these cells ties warm sensitivity and fever production to metabolic signaling. This detailed transcriptional analysis promises to provide important insight into the functioning of these critically important hypothalamic neurons.

### SP2.1

**About-hourly oscillations of body core temperature in small mammals.**

Refinetti R University of South Carolina - Circadian Rhythm Laboratory

Background: Virtually all mammals that have been studied so far have been found to exhibit daily/circadian oscillation in body core temperature. Many mammals also exhibit seasonal/circannual oscillation, which is especially conspicuous in hibernators. Surprisingly few studies have been dedicated to the investigation of hourly (ultradian) oscillations, and almost all of these failed to distinguish actual rhythmicity from artifacts produced by circadian rhythms.

Methods: Body temperature data were obtained by telemetry (with surgically-implanted radio transmitters) from three male individuals of each of seven species of small mammals under controlled laboratory conditions. The species were: flying squirrel, golden hamster, fat-tailed gerbil, Mongolian gerbil, degu, thirteen-lined ground squirrel, and tree shrew. Ultradian oscillatory components of body temperature were analyzed with standard procedures of time series analysis before and after filtering-out of the circadian component. Results: Body temperature exhibited daily and about-hourly oscillation in all species. Half-daily oscillation was also observed in some of the species. Whereas daily oscillation was always robust and statistically significant, about-hourly oscillation was randomly distributed. About-hourly oscillations detected by analysis of raw data were predominantly artifacts of spectral analysis in the detection of daily oscillation. Conclusion: Although about-hourly oscillation in the body temperature of small mammals is very common, the oscillatory pattern is not stationary and does not give rise to statistically significant ultradian rhythms in any of the seven species investigated in this study.
the default condition while heterothermy can result from many disturbances to energy or water balance.

Keywords: circadian rhythm, core temperature, free-ranging, heterothermy, mammal

SP3.1

The distributions of thermal and psychological sweating: challenging some persistent teachings. Taylor NAS, Machado-Moreira CA University of Wollongong – Centre for Human and Applied Physiology

Background: Past research has provided answers to many important questions. On closer examination, one finds some answers to be less convincing. Examples of this will be explored, and recent sudomotor research that encourages alternative interpretations will be presented.

Alternative interpretations: Five accepted teachings will be evaluated. (1) Early research described a dermatomal recruitment of sweating. However, re-examination of this evidence reveals that unequivocal support for that hypothesis is lacking. (2) The accepted teaching is that thermal and psychological sweating are modulated via separate neural pathways and neurotransmitters, and from different skin surfaces. Recent experiments demonstrate that psychological sweating to be ubiquitous, with no evidence for consistent differences between glabrous and non-glabrous skin. Indeed, correlations between psychological and thermal sweating were 0.83-0.89, with regional variations simply tracking the distribution of thermal sweating. Moreover, a blockade study with thermal clamping has challenged putative noradrenergic pathways. (3) Thermal and psychological stimuli are believed to have mutual inhibitory sudomotor influences. However, more detailed experiments failed to support these interactions. Indeed, thermal stimulation always facilitated psychological sweating. (4) During exercise, thermal sweating distribution was thought to be hierarchical, perhaps to optimise heat dissipation. Instead, elevated local sweating seems merely to reflect sites approaching their sweat production potential. (5) Finally, sweat redistribution following heat adaptation has been described. However, detailed investigation has shown this to be imprecise. Instead, sites further away from their potential experience the greatest increase in secretion.

Conclusion: The control of human sweating during thermal, psychological and exercise stresses appears to be much less complicated than past researchers have suggested.

Key words: psychological sweating, thermal sweating

SP3.2

Heat dissipation in grafted skin. Crandall CG University of Texas Southwestern Medical Center - Institute for Exercise and Environmental Medicine

In the United States, 40,000 to 70,000 individuals per year are hospitalized for burn-related injuries, and ~16% of these individuals (6,400-11,200/year) have burns covering more than 20% of their total body surface area (BSA). Twenty years ago burns covering half of a person’s BSA were often fatal. However, due to medical advances, patients with 90% BSA burned are now surviving these injuries. Thus, more individuals are living with larger percentages of BSA of grafted skin than ever before. Severe skin burns typically require that most or the entire dermal layer is excised. This area is then covered with donor skin harvested from other regions of the body. For split thickness grafts, which is the most common of the skin grafting techniques, all of the epidermis and a portion of the dermis are removed from a donor site and grafted to the debrided injured site. Thus, neural and vascular “connections” are disrupted by the grafting procedure. Well-healed grafted skin does not dilate nor sweat secondary to increases in internal temperature. While the capacity of grafted skin to increase blood flow to a local heating perturbation is partially preserved, sweating responses to exogenously administered sudorific agents remain non-functional. Given these altered responses, it is generally accepted that temperature regulation is impaired in skin graft recipients, depending on the BSA of grafted skin. However, experimental data supporting this hypothesis are mixed. Data will be presented addressing the implications and associated complications of grafted skin on heat dissipation in otherwise healthy humans.

SP3.3

Altered local mechanisms of cutaneous vasodilation and vasoconstriction in essential hypertension. Holowatz LA Penn State - Kinesiology

Background: Essential hypertension is a pro-inflammatory, pro-constrictor systemic vascular disease coinciding with endothelial dysfunction and inward vessel remodeling. Deficits in cutaneous microvascular reactivity including, augmented vasoconstriction (VC), and attenuated nitric oxide (NO)-dependent vasodilation are clearly evident in the skin of essential hypertensive humans but the mechanism underlying these changes are unclear.

Methods: In a series of protocols we have paired in vivo functional studies using intradermal microdialysis with local cooling and heating stimuli to isolate the Rho kinase (ROCK) and NO signaling pathways, respectively, and in vitro analysis of skin biopsies in essential hypertensive and age-matched normotensive humans.

Results: In response to local cooling the magnitude of the VC was similar between groups, but the hypertensive group relied almost exclusively on ROCK-dependent mechanisms. VD in response to local heating was reduced in the hypertensive group, and endothelial NO-dependent VD was augmented when the pro-inflammatory, oxidant stress promoting inducible NO-synthase (iNOS), or the arginase pathway was pharmacologically inhibited. iNOS expression was increased and the downstream vasodilatory target vasoactive stimulated phosphoprotein was decreased in skin from hypertensive humans. Conclusions: Augmented ROCK-dependent vasoconstrictor mechanisms, and the pro-inflammatory iNOS and arginase pathways contribute to cutaneous microvascular dysfunction in essential hypertensive
Inflammation Laboratory, 5UFMG – Physiology and Biophysics, 6St Joseph’s Hospital and Medical Center – Systemic Inflammation, Biophysics, 2St Joseph’s Hospital and Medical Center – Systemic Inflammation / Arizona State University – Bioengineering, 4St Joseph’s Hospital and Medical Center – Systemic Inflammation / UFAS – Physiology and Biophysics, 5St Joseph’s Hospital and Medical Center – Systemic Inflammation, 6Arizona State University – Bioengineering, 7St Joseph’s Hospital and Medical Center – Systemic Inflammation Laboratory, 8UFMG – Physiology and Biophysics, 9St Josephs Hospital and Medical Center – Systemic Inflammation

SP3.4
Is the body’s ability to dissipate heat compromised following exercise-induced heat stress? Kenny GP
University of Ottawa - School of Human Kinetics
Cutaneous vasodilation and sweating are critical responses necessary for effective thermoregulation during heat stress in humans. The ability to modulate the rate of heat loss through adjustments in vasomotor and sudomotor activity is a fundamental mechanism of thermoregulatory homeostasis. Studies suggest that recovery from dynamic exercise results in significant perturbations in thermoregulatory control in young healthy adults. These disturbances evoke a prolonged elevation in core body temperature and a concomitant reduction in skin blood flow and sweating. Core temperature set-point control theory states that elevations of skin blood flow and sweating proportional to elevations in core temperature should occur via a hypothalamic negative feedback loop in order to maintain an enhanced rate of heat loss. However, despite a persistent elevation in core body temperature, skin blood flow and sweating decreases in the early stages of recovery. This observation is consistent with a resetting of the core temperature-skin blood flow/sweating relationship. This apparent disturbance in post-exercise thermal homeostasis has been ascribed to nonthermal factors thought to be associated with post-exercise blood pressure regulation. This presentation will examine our current understanding of post-exercise thermoregulatory control. Data will be presented which evaluates the influence of thermal and nonthermal factors on whole-body loss during and following exercise as assessed by direct whole-body calorimetry.

SP4.1
Mapping a group of hypothalamic neurons that mediates cold-seeking behavior in endotoxin shock. Wanner SP, Almeida MC, Shimansky YP, Oliveira DL, Coimbra CC, Romanovsky AA
1St. Joseph’s Hospital and Medical Center – Systemic Inflammation / UFAS – Physiology and Biophysics, 2St. Joseph’s Hospital and Medical Center – Systemic Inflammation, 3Arizona State University – Bioengineering, 4St. Joseph’s Hospital and Medical Center – Systemic Inflammation Laboratory, 5UFMG – Physiology and Biophysics, 6St Josephs Hospital and Medical Center – Systemic Inflammation

The dorsomedial hypothalamus (DMH) is an important brain site for the regulation of many autonomic, endocrine, and behavioral functions. Within the DMH, neurons in the dorsal hypothalamic area (DA) are implicated in the neural pathway that activates brown adipose tissue thermogenesis, an autonomic thermoeffector recruited to defend body temperature against cold. In the past, we found that some DMH neurons were essential for triggering cold-seeking behavior during lipopolysaccharide (LPS)-induced shock, but the precise location of these neurons was unknown. The present experiments were aimed at investigating the DMH topography for LPS-induced cold-seeking response and comparing it with the topography for the autonomic defense of body temperature against cold. Small (300 – 1,000 mm) thermal (radio frequency) lesions were placed in different parts of the DMH area in 83 rats. Effects of lesions on the cold-seeking response to a high dose of LPS (5,000 mg/kg i.v.) were studied in a thermogradient apparatus where rats moved freely to select their preferred ambient temperature. Effects on the autonomic cold-defense response were studied in restrained rats exposed to 4°C. For each response, a functional 3D map of the DMH area was compiled. The area mediating the cold-seeking response to LPS was found to include a ventrocaudal portion of the dorsomedial hypothalamic nucleus (DMN) and a dorsal portion of the ventromedial hypothalamic nucleus. The area controlling the autonomic cold-defense response was located more dorsally and more rostrally: in the DA and at the dorsal border of the DMN adjacent to the DA. To confirm that disappearance of the cold-seeking response to LPS in rats with thermal lesions was due to the loss of neuronal bodies (not of fibers of passage), we placed small chemical lesions in the newly identified area at the ventrocaudal border of the DMN by using ibotenic acid. Rats with chemical lesions to this area did not seek for a cold environment when subjected to LPS shock, but their autonomic cold defense was not compromised. We conclude that cold-seeking behavior in LPS shock is mediated by a small group of neurons at the ventrocaudal border of the DMN.

SP4.3
Mice modulates behavioral thermoregulation in heat during plasma hyperosmolality and the influence of daily activity. Nagashima K
1Waseda University – Integrative Physiology – Active Life
We evaluated the effect of plasma hyperosmolality on behavioral thermoregulation in mice. Experiment system consisted of Plexiglas box (dimensions: 50×12×19 cm) with five Peltier boards at the bottom. Experiments were conducted in two different settings. An operant behavior setting: boards were first set to 39°C, and one board was changed to 20°C for 1 min when a mouse moved to a specific position. A temperature mosaic setting: each board was randomly set to 15°C, 22°C, 28°C, 35°C, or 39°C with a 6-min interval, but each board temperature was different from the others at a given time point. Mice were injected s.c. isotonic or hypertonic saline (154 mM (IS group) or 2,500 mM (HS group), 10 ml/kg body wt), and exposed to either setting for 90 min. The same experiments were conducted in the mice with free access to running wheel (IS-W and HS-W groups). In the operant setting, the HS group showed fewer operant behavior counts than the IS group (11 vs. 5 and 25 vs. 4 counts, respectively; P<0.05) with greater increase in body temperature (1.6 °C vs. 0.0 °C, respectively; P< 0.05). In the mosaic setting, the HS group selected...
the board temperature of 35°C more frequently than the other temperatures (P<0.05) with the same increase in body temperature. Such differences were not observed between the IS-W and HS-W groups. These results may suggest that plasma hyperosmolality modulates behavioral thermoregulatory response to heat and induce regulated hyperthermia, and the modulation was abolished after daily spontaneous exercise.

**SP4.4**

Thermal perception during heat is modulated by plasma hyperosmolality and its comparison between trained and non-trained young men. Tokizawa K1, Nakamura M2, Uchida Y1, Lin GH1, Nagashima K4 - 1Sport Science Center for Active Life – Faculty of Sport Sciences – Laboratory of Integrative Physiology, 2Laboratory of Integrative Physiology – Faculty of Human Sciences – School of Health Sciences – University of Wollongong, 3Faculty of Human Sciences – Laboratory of Integrative Physiology, 4Faculty of Human Sciences, Waseda University – Integrative Physiology (Body fluid and temperature)

The thermal perception evoked by thermal stimulation can be divided into two categories, “thermal sensation” and “thermal pleasantness”. Thermal sensation is thermal information regarding external objects or the environment, which is obtained by the warm or cold receptors in the skin. In contrast, thermal pleasantness is affected by information from the skin and body core temperature. Between the two thermal perceptions, thermal pleasantness would be more important in activating behavioral thermoregulation. The thermoregulatory system interacts with other functional systems. For example, with the body fluid regulatory system, excessive sweating induces dehydration, which subsequently impairs autonomic thermoregulation (i.e. decreases in sweat rate and skin blood flow in the heat). We sought to evaluate whether this interaction extends behavioral thermoregulation, i.e. thermal perceptions.

Dehydration was induced by exercise in heat or hypertonic saline infusion. To analyze thermal perceptions, skin temperature was controlled by ambient temperature changes or water-perfused suits. Thermal sensation to skin temperature increases was shaped increase on TB (5.0h: Rectal = -0.1±0.1; Tail: Vehicle = 0.0±0.1; ANA = 1.2±0.1). Warm tail skin temperature (4.0h Rectal: Vehicle = -0.1±0.1; ANA = 1.2±0.1; Tail: Vehicle = 0.0±0.1; ANA = -0.7±0.1°C). The CB1 agonist ACEA induced a bell shaped increase on TB (5.0h: Saline = 0.1±0.0; ACEA 0.001mg = 0.6±0.2; ACEA 0.01mg = 1.4±0.1; ACEA 0.1mg = 0.8±0.2; ACEA 1.0mg = 0.6±0.1°C). I.c.v injection of CB2 agonist AM1241 did not induce change on TB. The i.c.v. pre-treatment with the CB2 antagonist AM251, reduced the fever induced by i.c.v injection of anandamide 1.0mg (5.0h: Saline/AN A = 0.1±0.1; AM251 10.0mg/Vehicle = 0.2±0.1; Vehicle/ANA 1.0mg = 1.8±0.1; AM251 10.0mg/ANA 1.0mg = 0.6±0.2; AM251 5.0mg/ANA 1.0mg = 0.4±0.1; AM251 1.0mg/ANA 1.0mg = 1.6±0.2°C). Pre-treatment of the animals with AM251 5.0mg reduced the fever induced by ACEA 0.01mg (5.0h: AM251/Saline = 0.1±0.1; Saline/ACEA = 1.5±0.1; AM251/ACEA = 0.5±0.1°C). Pre-treatment of the animals with AM251 5.0mg, i.c.v. reduced the fever induced by LPS 50.0 mg/kg, i.p. (48%). Pre-treatment of the animals with the non-selective cyclooxygenase (COX) inhibitor, ibuprophen 10.0mg/kg, i.p., selective COX-2 inhibitor celecoxib 5.0mg, p.o., or IL-1ra 200mg, i.c.v. reduced the fever of anandamide 1.0mg, i.c.v. (53%, 40% and 67% respectively). Pre-treatment of the animals with the non-selective opioid antagonist naloxone 1.0mg/kg, s.c. abolished the fever induced by anandamide 1.0mg, i.c.v. Conclusions: These results suggest that endogenous cannabinoids, through the activation of CB1 receptor, are important mediators involved in the development of fever, and that endocannabinoids induce fever through the synthesis/release of prostaglandin and opioids.

**SP5.2**

Anandamide-induced fever is dependent on prostaglandins, opioids, and interleukin-1. Fraga D1, Silva CZ2, Parada CA2, Souza GEP3 - 1UFPR – Pharmacology, 2FMRP-USP – Pharmacology, 3FCFRP-USP

Aim: The present work aimed to investigate the contribution of the endogenous cannabinoids on fever. Methods: Changes in rectal temperature of male Wistar rats were measured in a 30 min interval up to 6 h. Results: I.c.v. administration of anandamide (ANA) induced a dose dependent increase on body temperature (TB 4.0h: Vehicle = -0.0±0.1; ANA 0.01mg = 0.4±0.1; ANA 0.1mg = 0.9±0.1; ANA 1.0mg = 1.5±0.0; ANA 10.0mg = 1.5±0.1°C), this increase on TB induced by anandamide was followed by a decrease on tail skin temperature (4.0h Rectal: Vehicle = -0.1±0.1; ANA = 1.2±0.1; Tail: Vehicle = 0.0±0.1; ANA = -0.7±0.1°C). The CB1 agonist ACEA induced a bell shaped increase on TB (5.0h: Saline = 0.1±0.0; ACEA 0.001mg = 0.6±0.2; ACEA 0.01mg = 1.4±0.1; ACEA 0.1mg = 0.8±0.2; ACEA 1.0mg = 0.6±0.1°C). I.c.v injection of CB2 agonist AM1241 did not induce change on TB. The i.c.v. pre-treatment with the CB2 antagonist AM251, reduced the fever induced by i.c.v injection of anandamide 1.0mg (5.0h: Saline/ANA = 0.1±0.1; AM251 10.0mg/Vehicle = 0.2±0.1; Vehicle/ANA 1.0mg = 1.8±0.1; AM251 10.0mg/ANA 1.0mg = 0.6±0.2; AM251 5.0mg/ANA 1.0mg = 0.4±0.1; AM251 1.0mg/ANA 1.0mg = 1.6±0.2°C). Pre-treatment of the animals with AM251 5.0mg reduced the fever induced by ACEA 0.01mg (5.0h: AM251/Saline = 0.1±0.1; Saline/ACEA = 1.5±0.1; AM251/ACEA = 0.5±0.1°C). Pre-treatment of the animals with AM251 5.0mg, i.c.v. reduced the fever induced by LPS 50.0 mg/kg, i.p. (48%). Pre-treatment of the animals with the non-selective cyclooxygenase (COX) inhibitor, ibuprophen 10.0mg/kg, i.p., selective COX-2 inhibitor celecoxib 5.0mg, p.o., or IL-1ra 200mg, i.c.v. reduced the fever of anandamide 1.0mg, i.c.v. (53%, 40% and 67% respectively). Pre-treatment of the animals with the non-selective opioid antagonist naloxone 1.0mg/kg, s.c. abolished the fever induced by anandamide 1.0mg, i.c.v. Conclusions: These results suggest that endogenous cannabinoids, through the activation of CB1 receptor, are important mediators involved in the development of fever, and that endocannabinoids induce fever through the synthesis/release of prostaglandin and opioids.

**SP5.3**

Central CB1 receptors mediate initiation of hypotension during septic shock. Feleder C1, Millington W1, Villanueva A1, Yilmaz S2, Cheer J1, Parsons S1 - 1Albany College of Pharmacy and Health Sciences – Pharmaceutical Sciences, 2Uludag University – Pharmacology and Clinical Pharmacology, 3University
It is generally taken for granted that lipopolysaccharide (LPS) decreases arterial blood pressure during septic shock by stimulating the release of vasoactive mediators, such as, tumor necrosis factor-α (TNF) and other substances produced by macrophages, and that TNF reduces arterial blood pressure by increasing nitric oxide synthesis and release, which triggers the vasodilation. New studies from our and other laboratories have shown that LPS-induced hypotension can be precluded by impeding afferent signaling flow in the vagus nerve, by inhibiting neuronal activity in the nucleus of the solitary tract or by blocking alpha- adrenergic receptors in the preoptic area/anterior hypothalamic area (POA). These findings suggest that LPS-induced shock may be initiated by a central mechanism that involves the activation of the POA neuronal circuits. Thereafter, we tested whether central cannabinoid-1 (CB1) receptors contribute to the control of the initiation of LPS-hypotension, supported on substantial information that hypothalamic neurons express CB1 receptors and synthesize the endogenous cannabinoid anandamide. We found that the central administration of rimonabant, a CB1 receptor antagonist, blocked the decrease in arterial blood pressure induced by LPS drastically in both conscious and unconscious rats. Rimonabant inhibited the rapid initial fall in arterial pressure induced by LPS and the late, delayed hypotensive phase that eventually leads to organ failure and death. Rimonabant blocked LPS-induced norepinephrine (NE) release in the POA implying that the CB1 antagonist prevents initiation of LPS hypotension by inhibiting the release of NE in the POA. Interestingly, rimonabant also prevented the delayed increase in plasma TNF levels induced by LPS. This study shows that central CB1 receptors mediate LPS hypotension.

**SP.5.4**

Lipopolysaccharide-induced hypothermia critically depends on brain CB1 receptors. Steiner AA1, Molchanova2, Dogan M2, Patel S3, Pátervári E4, Balaskó M4, Wanner SP3, Eales J5, Oliveira DL6, Gavva NR7, Almeida MC8, Székely M9, Romanovsky AA1, 1St. Joseph’s Hospital – Albany College of Pharmacy and Health Sciences, 2St. Joseph’s Hospital– Institute of Physiology, Minsk, Belarus, 3St. Joseph’s Hospital, 4University of Pécs, 5St. Joseph’s Hospital, 6Amgen Inc, 7University of Pécs

**Background:** Systemic inflammation and related disorders, including sepsis, are leading causes of death in hospitalized patients. In most severe cases, systemic inflammation is accompanied by a drop in body temperature (hypothermia). We know that inflammation-associated hypothermia is a brain-mediated response, but mechanisms of this response are unknown. **Methods and results:** We administered bacterial lipopolysaccharide to rats to cause systemic inflammation and hypothermia. We then used a variety of pharmacological tools to probe whether three different receptors are involved in this hypothermia. We have found that one of the receptors studied, the so-called cannabinoid-1 (CB1) receptor, is crucial for the development of hypothermia. This is the same receptor that is responsible for many effects of marijuana (cannabis). We further show that hypothermia associated with inflammation depends on CB1 receptors located inside the brain. **Conclusion:** These findings suggest that the brain CB1 receptor should be studied as a potential therapeutic target in systemic inflammation and sepsis. **Key words:** Hypothemia, inflammation, cannabinoids. **Support:** NIH (R01NS41233 to AAR); OTKA (49321 to MS); OTKA (PD-84241 to EP)

**SP.6.1**
The putative JAK-STAT inhibitor AG490 and the putative NFkappaB inhibitor parthenolide show differential effects on fever and brain inflammatory markers during LPS-induced systemic inflammation in rats. Damm J1, Harden L2, Gerstberger R3, Hübbschle T4, Roth J5, Rummel C6, Justus-Liebig-University Giessen, Germany – Veterinary Physiology and Biochemistry, 2University of Witwatersrand, – Brain Function Research Group, School of Physiology

**Background/aims:** Although a pivotal role for inflammatory transcription factors, such as signal transducer and activator of transcription (STAT3), nuclear factor (NF)kB and NF-interleukin(IL)6, has been proposed during brain inflammation, the functional significance of their contribution to the induction of brain controlled sickness responses such as fever during infection and inflammation is unknown. **Methods:** Thus we used AG490 a broadly used JAK-STAT inhibitor and the putative NFxkB inhibitor Parthenolide (P) to further elucidate the role of inflammatory transcription factors on sickness behavior, fever and accompanying brain inflammation induced by systemic injection of lipopolysaccharide (LPS, 100µg/kg). **Results:** AG490 pretreated animals showed modestly exaggerated fever, attenuated adipsia and no lethargy compared to LPS-controls while P-pretreated animals showed a decreased febrile response to LPS. In the hypothalamus, markers of NFkB / NF-IL6 pathway activation and NFkB immunoreactivity were significantly reduced 8 h after LPS-stimulation by P pretreatment but remained unchanged when using AG490 pretreatment. In summary, we have shown dissociation between the effects of central AG490 treatment on fever and sickness behavior, which appears to be related to reduced IL-10 and increased mPGES expression in the brain. In contrast, P attenuates the febrile response during LPS-induced systemic inflammation by reducing the circulating cytokines IL-6 and TNFα and decreasing the hypothalamic NFxB / NF-IL6 activation and expression of COX2. **Conclusion:** These results suggest a therapeutic potential for P to reduce brain inflammation and for AG490 to reduce sickness behavior without influencing the beneficial effects of fever during systemic inflammation. **Key words:** inflammatory transcription factors, sickness behavior, prostaglandins, cytokines, lipopolysaccharide
SP6.2
Role of chemokines and its receptors on the CNS for inducing fever response. Soares DM1, Ott D2, Souza GEP3, Roth J1 – 1 FCFRP-USP – Pharmacology / UFBA – Pharmacology, 2Justus-Liebig University – Veterinary Physiology, 3FCFRP-USP – Pharmacology

Chemokines are relatively low molecular mass proteins (8–10 KDa) that have chemotactant effects on many cell types expressing their corresponding receptors, and thus play a critical role in immune surveillance. Among their functions, it has been shown that chemokines, in particular, Macrophage Inflammatory Protein (MIP)-1 a and b, Cytokine Induced NeutrophilChemoattractant (CINC-1) and regulated on activation, normal T cells expressed and secreted (RANTES), act as endogenous pyrogens when injected into the CNS of rats. Although studies have shown that chemokines are pyrogenic when injected into the brain, there is no data indicating which cells or receptors in the CNS chemokines such as RANTES and MIP-1α act to induce fever in rats. We have shown that RANTES depends on prostaglandin synthesis for evoking fever, while MIP-1α does not. Moreover, it has been suggested that RANTES is involved in mediating LPS-induced fever, while MIP-1α is not. Both RANTES and MIP-1α can bind to the receptors CCR1 and CCR5 which are expressed on neurons, microglia and astrocytes in the CNS. Based on these observations we hypothesized that RANTES and MIP-1α can differently activate neurons, microglia or astrocytes in the AH/POA through CCR1 and CCR5, which in turn RANTES and MIP-1α can differently activate those cells what results on synthesis/release of pyrogens (CRF, TNFa, e IL-6) for fever induction. We found that those chemokines are able to induce Ca2+ mobilization in the cells of the preoptic area of the hypothalamus in the absence of cytokine production, which is commonly noted when these cells are stimulated with LPS. Based on the above mentioned, we can assume that chemokines and chemokine receptors have an important, but yet unknown role in mediating fever in the CNS. Therefore, the chemokine system deserves more investigations to clarify the function it plays in the febrile response.

SP6.3
Peripheral-released Interleukin-10 and immune-to-brain signaling in mediating lipopolysaccharide-induced fever. Harden L1, Rummel C2, Damm J3, Laburn HP1, Wiegand F3, Poole S2, Gerstberger R2, Roth J1 - 1University of the Witwatersrand – Brain Function Research Group, 2Justus-Liebig-University Giessen, – Veterinary-Physiology and -Biochemistry, 3National Institute for Biological Standards and Control, Potters Bar – Biotherapeutics group

Background/Aims: Peripheral-released interleukin-10 (IL-10) has been implicated as an endogenous mediator involved in limiting fever, due to its capacity to inhibit the production of IL-6. The endogenous antipyretic action of IL-10 may not only be related to its inhibitory action on cytokine production, but also on prostanoid production, in particular prostaglandin E2 (PGE2), a key terminal mediator of fever. Using a technique, which allows selective blockade of endogenous IL-10, we aimed to characterize the actions by which peripherally-released IL-10 regulates cytokine and prostanoid production in the periphery and the brain, during a severe form of infection. Methods: Male Wistar rats were randomly assigned to receive IL-10 antiserum (IL-10AS) or normal sheep serum intraperitoneally (i.p.), 4 h before receiving an i.p. injection of lipopolysaccharide (LPS) (10 mg/kg) or phosphate-buffered saline (PBS). We measured the effect of neutralizing peripherally-released IL-10 on LPS-induced fever, and the suite of pro-inflammatory mediators known to induced fever, such as IL-1beta, IL-6, tumour necrosis factor-alpha (TNF-alpha), PGE2 and the rate limiting enzymes required for PGE2 synthesis, namely cyclooxygenase (COX-2) and microsomal PG synthase -1 (mPGES-1). Results: Administration of LPS induced an initial period of hypothermia (~1°C), which lasted for ~2 h, after which a fever developed. Pre-treating rats with IL-10AS significantly attenuated the period of hypothermia and increased the amplitude (~0.4°C) of the fever. Moreover, IL-10AS pre-treatment augmented the LPS-induced increase in plasma levels of TNF-alpha, IL-6, IL-1beta and PGE2 over the duration of the fever. LPS-induced mRNA levels of TNF-alpha, IL-6, IL-1beta and COX-2 showed a time-dependent augmentation in the liver and spleen. Conclusion: Our data support a time-dependent regulatory role for peripherally-released IL-10 in limiting the amplitude of fever, due to its inhibitory activity on cytokine and prostanoind production primarily in the liver, spleen and circulation during severe Gram-negative bacterial infections.

SP6.4
Antipyretic effect of dipyrone metabolites in the fever induced by LPS and Tityus serrulatus venom (Tsv). Malvar DC1, Vaz, LLV1, Figueiredo Mu1, Melo MCC1, Clososki GC1, Souza GEP1– FCFRP/USP – Physic and Chemistry

Background/Aim: 4-methylaminoantipyrine (4-MAA) and 4-aminoantipyrine (4-AA) are regarded the antipyretic metabolites of dipyrone by blocking cyclooxygenases (FASB E J. 21:2543, 2007). However, dipyrone abolishes the PGE2-independent fever induced by Tsv (Toxicon. 48:556, 2006) and its antipyretic effect is unrelated to PGE2 synthesis inhibition in the hypothalamus after endotoxin-1 and LPS (Br J Pharmacol. 162:1401, 2011). Here we compared the antipyretic effect of dipyrone metabolites, 4-MAA, 4-AA, 4-formylaminoantipyrine (4-FAA) and 4-acetylaminoantipyrine (4-AAA), on LPS- and Tsv-induced fever. Methods: Male Wistar rats (200g) received saline, dipyrone, 4-MAA, 4-AA, 4-AAA (60-360mg kg−1) or 4-FAA (120-360mg kg−1) i.p. 30 min before the i.p. injection (0.5 ml) of LPS (50 g kg−1), Tsv (150 g kg−1) or saline. Body temperature was measured for up 6 h by telemetry. Results: At low dose (60-120mg kg−1) dipyrone reduces LPS- and Tsv-induced fever. At high dose (240-360mg kg−1) it induces hypothermia. Low doses (60-90mg kg−1) of 4-MAA or 4-AA or high doses (240-360mg kg−1) of 4-FAA, but not 4-AAA produced a dose-related inhibition on LPS-
immunofluorescence. ELISAs and immunohistochemistry / mediators was analyzed by RT-PCR, bioassays, brain-intrinsic (hypothalamic) induction of inflammatory were recorded by telemetric devices. Peripheral and Body temperature, motor activity, food and water intake were again to a higher degree in s.c. treated rats.

Corresponding to the peripheral induction of IFNg and / or IL-6, imiquimod caused stronger activation of NF-IL6, while the IL-6 mediated nuclear translocation of STAT3 was more pronounced in response to ODN 1668. Conclusion: Even when given at a high dose, imiquimod and ODN 1668 cause rather moderate brain-inflammatory responses, which are related to peripheral IFN / IL-6-expression and possibly mediated by brain-intrinsic activation of NF-IL6 / STAT3 and the induction of a proinflammatory cocktail within the hypothalamus. Compared to other TLR-agonists, brain-controlled illness responses are rather moderate after s.c. or i.p. treatment of rats with imiquimod or ODN 1668. The lack of a septic state in imiquimod or ODN 1668-treated rats reinforces therapeutic use of these drugs. Key words: Fever, Toll-like receptors, cytokines, transcription factors, immune-to-brain signaling

SP.6.5

Sickness- and brain inflammatory responses of rats induced by systemic and localized stimulation with specific agonists of the endosomal Toll-like receptors 7 and 9. Roth J¹, Damm J², Wiegand F³, Harden L⁴, Gerstberger R², Rummel C¹

University of Giessen – Veterinary-Physiology and -Biochemistry, ²Justus-Liebig-University Giessen, Germany – Veterinary-Physiology and Biochemistry, ³Justus-Liebig-University Giessen Germany – Veterinary Physiology, ⁴University of Witwatersrand – Brain Function Research Group, School of Physiology

Background / Aims: Toll-like receptors (TLRs) of the innate immune system recognize conserved molecular patterns associated with microbial pathogens. TLRs 7 and 9 are located in the endosomal compartments due to their task to sense single stranded viral RNA (TLR7) or intracellular bacterial or viral CpG-DNA. The synthetic TLR7 and TLR9 agonist imiquimod and ODN 1668 are used as immuoadjuvants or for topical treatment of skin cancers. According to these circumstances detailed information about possible side effects of these drugs are warranted. Therefore, the consequences of local subcutaneous (s.c.) or systemic intraperitoneal (i.p.) injections of imiquimod / ODN 1668 on the manifestation of fever, sickness behaviour, and the peripheral and brain-intrinsic induction of a variety of inflammatory molecules were investigated in rats.

Methods: Rats were given s.c. (subcutaneous air pouch) or i.p. imiquimod / ODN 1668 (1 or 5 mg kg⁻¹). Body temperature, motor activity, food and water intake were recorded by telemetric devices. Peripheral and brain-intrinsic (hypothalamic) induction of inflammatory mediators was analyzed by RT-PCR, bioassays, ELISAs and immunochemistry / immunofluorescence. Results: Imiquimod and ODN 1668 are the first TLR-agonist investigated, which have stronger effects on fever and anorexia after its s.c. as compared to i.p. administration. Peripheral induction of interferons (IFNs) and putative circulating pyrogens (TNF, IL-6) corresponded to the strength of the illness responses. While imiquimod showed stronger capacities to induce IFNs, namely IFNg, ODN 1668 induced higher levels of circulating IL-6. In the brain (hypothalamus), an expression of cytokines (TNFa, IL-1b, and IL-6) and inducible forms of enzymes for prostaglandinE2 synthesis (COX-2, mPGES), occurred, which was accompanied by a moderate activation of the transcription factors NFkB and STAT3 and a strong activation of the transcription factor NF-IL6, namely in cells of specific sites with an open blood-brain barrier, again to a higher degree in s.c. treated rats. Corresponding to the peripheral induction of IFNg and / or IL-6, imiquimod caused stronger activation of NF-IL6, while the IL-6 mediated nuclear translocation of STAT3 was more pronounced in response to ODN 1668. Conclusion: Even when given at a high dose, imiquimod and ODN 1668 cause rather moderate brain-inflammatory responses, which are related to peripheral IFN / IL-6-expression and possibly mediated by brain-intrinsic activation of NF-IL6 / STAT3 and the induction of a proinflammatory cocktail within the hypothalamus. Compared to other TLR-agonists, brain-controlled illness responses are rather moderate after s.c. or i.p. treatment of rats with imiquimod or ODN 1668. The lack of a septic state in imiquimod or ODN 1668-treated rats reinforces therapeutic use of these drugs. Key words: Fever, Toll-like receptors, cytokines, transcription factors, immune-to-brain signaling

SP.7.1

Molecules regulating temperature in response to calorie intake. Conti B The Scripps Research Institute - Molecular and Integrative Neurosciences Department

The mechanisms by which calorie intake can influence core body temperature remain poorly understood. We present data showing the warm sensitive neurons of the preoptic area express receptors for nutrient signals and that their activation or expression level affect core body temperature. These include the receptors for insulin, adiponectin and an orphan G-protein coupled receptor.

SP.7.2

Early inflammation: programming adult innate and metabolic pathways. Pittman QJ University of Calgary - Hotchkiss Brain Institute

When rodent pups at postnatal day 14 are exposed to the TLR4 ligand, LPS, or the TLR3 ligand, Poly I:C they develop short monophasic fevers. When they are exposed to these inflammatory molecules as adults, the febrile and pro-inflammatory cytokine response, as well as the induction of COX-2 in the brain are reduced if the same inflammatory molecules is used. That is responses to LPS in LPS treated pups is reduced and that to Poly I:C in Poly I:C treated pups is reduced. However, if the pups are exposed to one inflammatory molecule, responses to the other molecule are unaltered. With a focus for changes possibly residing in the toll like receptors, we quantified TLR3 and TLR4 mRNA in the liver and spleen of the adult. Both were elevated if there had been previous pup exposure to its ligand but not if the previous exposure had been to a different ligand. To assess the contribution of elevated TLR mRNA to a reduced febrile and pro-inflammatory response, we measured circulating corticosterone in the adult and found that it was elevated early after LPS, but not at later stages of the fever in pre-exposed pups. To determine the possible mechanisms underlying the enhanced early corticosterone response we measured COX-2 in the liver and found it to be constitutively elevated. When LPS was given neonatal LPS treated adults had increased levels of PGE2 in the circulation that is most likely responsible for the early corticosterone rise, as this is prostaglandin dependent.
SP7.3
Metabolic signals & the fever-hypothermia dichotomy in systemic inflammation. Steiner AA\textsuperscript{1}, Krall CM\textsuperscript{2}, Feleder C\textsuperscript{1}, Hass MA\textsuperscript{2}, Yao X\textsuperscript{1}  
\textsuperscript{1}Albany College of Pharmacy and Health Sciences – Pharmaceutical Sciences,  
\textsuperscript{2}Albany College of Pharmacy and Health Sciences – Arts and Sciences

Background: The state of energy balance has been shown to influence body temperature \((T_b)\) responses in systemic inflammation, but the mechanisms involved are unknown. We tested the hypothesis that food deprivation enhances inflammatory signaling that decreases \(T_b\) (cryogenic signaling) while having little effect on inflammatory signaling that increases \(T_b\) (febrigenic signaling).

Methods: Food-deprived (24 h) or free-feeding rats were intravenously injected with lipopolysaccharide (LPS) at doses (500 and 2,500 \(\mu\)g/kg) known to activate both febrigenic and cryogenic signaling. These two types of signaling were dissected out in experiments conducted at different ambient temperatures: at 30\(^\circ\)C, \(T_b\) reflects mainly the actions of signaling. These two types of signaling were dissected

Results: Food deprivation had little effect on the fever induced by LPS at 30\(^\circ\)C, but enhanced the hypothermia induced by LPS at 22\(^\circ\)C. Enhancement of hypothermia was not due to thermogenic incapacity, since food-deprived rats were fully capable of raising \(T_b\) in response to the thermogenic drug CL316,243 (1 mg/kg, iv). Neither was enhancement of hypothermia associated with altered plasma levels of pro-inflammatory cytokines (TNF-alpha, IL-1beta and IL-6). The levels of prostaglandin (PG) \(D_2\) and \(PGE_2\) during LPS hypothermia were augmented by food deprivation, though the ratio between them remained unchanged. Food deprivation, however, selectively augmented the responsiveness of rats to the cryogenic action of \(PGE_2\) (100 ng, iv), without altering the responsiveness to febrigenic \(PGE_2\) (100 ng, iv). Conclusion: The results of the study support our hypothesis and suggest that augmented cryogenic signaling via \(PGE_2\) may underlie enhancement of LPS hypothermia by food deprivation.

Key words: energy balance, fasting, inflammation, fever, hypothermia. Support: Albany College of Pharmacy; National Institutes of Health

SP7.4
The effects of diet induced obesity on the febrile response to LPS. Luaheshi GN\textsuperscript{1}, Pohl J\textsuperscript{1}, Woodside B\textsuperscript{2}  
\textsuperscript{1}McGill University – Psychiatry,  
\textsuperscript{2}Concordia University

Obesity is often accompanied by a basal low-grade inflammatory state, a condition that has been linked to the development of secondary ailments such as Type II diabetes, cardiovascular diseases and rheumatoid arthritis. The specific mechanisms are unknown but some have suggested a connection with higher than normal levels of the circulating inflammatory mediators, cytokines. Using diet induced obese rats we have recently reported a significant alteration in the immune response to an acute injection of the bacterial immunogen Lipopolysaccharide (LPS). These changes included a fever response of a significantly higher magnitude and longer duration, as well as changes in other acute sickness type behaviours in obese Vs Lean controls. The alteration in the behavioural outcomes in the obese animals were accompanied by a higher than normal increases in cytokine release and expression, in the circulation, white adipose tissue and hypothalamic centres in the brain. In addition to cytokines such as interleukin-1 and 6 we detected a significant increase in LPS induced leptin levels in the circulation of obese animals, which appeared to correlate with the exacerbated inflammatory response reported in obesity which could contribute to the development of the more chronic diseases associated with this condition in humans.

SP7.5
Calorie restriction and its impact upon the behavioural, physiological, and metabolic indicators of illness in rats. Kent S La Trobe University – Psychological Science

Calorie restriction (CR) increases the mean and maximum lifespan; however, limited research has investigated the impact of CR on sickness behaviour (fever, anorexia, decreased locomotor activity). Previously we demonstrated that a 50\% CR for 28 days fully attenuates lipopolysaccharide (LPS)-induced sickness behaviour in mice. This attenuation was due to a central anti-inflammatory bias; hypothalamic immune markers (COX-2, mPGES-1, IL-10) shifted from their normal pro-inflammatory bias to an anti-inflammatory bias. The aim was to explore the relationship between CR and behavioural, physiological, and metabolic indicators of illness. A 50\% CR for 28 days in rats attenuated fever and sickness behaviour post-LPS. CR animals demonstrated no increase in body temperature \((T_b)\), limited reductions in locomotor activity, limited weight loss, and no reduction in food intake. At 2 hours post-LPS, serum corticosterone was increased and the normal increase in IL-6 was attenuated in the CR rats compared to controls. Rats CR to 50\% for 28 days demonstrated reduced metabolic rate and the expected increase post-LPS did not occur. When allowed to behaviourally thermoregulate in a thermocline the CR rats selected a higher ambient temperature \((T_a)\) compared to control rats, which resulted in a mild fever; however, other measures of sickness behaviour remain attenuated. These findings suggest that a 50\% CR leads to altered inflammatory pathways (a bias towards anti-inflammatory). The observation that CR rats self-select a \(T_a\) that resulted in an increased \(T_b\) suggests that it is the metabolic cost of raising their \(T_b\) that prevented their doing so in their normal environment.

SP8.1
Facultative thermogenesis: the lessons from mouse studies. Nedergaard J (Stockholm University, Sweden)

The recent insight that a substantial number of adult humans possess active brown adipose tissue has rendered insights from studies of animal thermogenesis timely and broadly important. Brown adipose tissue is
energy expenditure in humans. Cold activated brown adipose tissue and whole body nonshivering thermogenesis. However, from these data provide a relation between BAT FDG-uptake and energy expenditure measured by indirect calorimetry. The available studies at best FDG-PET/CT scans and energy expenditure measured correlations between BAT activity as measured by FDG-PET/CT scans can improve our estimation of BAT thermogenesis.

First the different cold exposure protocols will be discussed, ranging from air cooling, water cooling (tube suit), to ice cooling.

SP 8.2

Cold activated brown adipose tissue and whole body energy expenditure in humans. Van Marken Lichtenbelt WD – NUTRIM School for Nutrition, Toxicology and Metabolism – Maastricht University Medical Center – Human Biology.

The incidence of the metabolic syndrome has reached epidemic levels in the Western world. Therefore the recent identification of functional brown adipose tissue (BAT) in adult humans and its heat production capacities promoted a renewed interest in this tissue. In animals the contribution of BAT to the heat balance and energy metabolism is significant and relatively well described. The contribution of BAT thermogenesis in humans is much less clear.

Sustainable nonshivering thermogenesis in adult humans amounts to 15 percent of the average daily energy metabolic rate. Up to this day, dedicated studies on human cold activated BAT combined with measurements on energy expenditure are restricted to 6 studies. First the different cold exposure protocols will be discussed, ranging from air cooling, water cooling (tube suit), to ice cooling.

Secondly, attention will be given why not all studies find correlations between BAT activity as measured by FDG-PET/CT scans and energy expenditure measured by indirect calorimetry. The available studies at best provide a relation between BAT FDG-uptake and nonshivering thermogenesis. However, from these data the contribution of BAT thermogenesis is hard to quantify. Prudent calculations based on maximal BAT oxygen consumption in rodents combined with allometric considerations, and based on FDG-PET/CT scans reveal a contribution of activated BAT to 5% of basal metabolic rate. However, the calculations strongly depend on several assumptions made. New information on BAT activity from dynamic PET/CT scans can improve our estimation of BAT thermogenesis.

SP 8.3

Bilateral neural communication between the brain and BAT. Bartness TJ Georgia State University – Biology.

Brown adipose tissue (BAT) thermogenesis is innervated by the sympathetic nervous system (SNS) and activation of this innervation is the principal stimulator of thermogenesis by BAT. We defined the central origins of the SNS outflow to BAT using the transneuronal tract tracer, pseudorabies virus (PRV) previously as well as colocalization of BAT SNS outflow neurons with melanocortin receptor-4 receptor (MC4-R) mRNA finding high colocalization levels (~60%) across the neuroaxis. The hypothalamic paraventricular nucleus (PVH) was one of these areas and we tested the ability of MC4-R agonism to increase IBAT temperature (T IBAT) using telemetric thermists implanted under the interscapular BAT (IBAT) pad. Microinjection of the MC3/4-R agonist, melanotan II (MTII) into the PVH of freely moving Siberian hamsters significantly increased T IBAT compared with the vehicle. We also identified a new node in the SNS outflow to BAT, the subZonaincerta (subZI) also with high SNS outflow neuron co-localized MC4-mRNA. Microinjections of the MTII or the specific MC4-R agonist, cyclo [ß-Ala-His-D-Phe-Arg-Trp-Glu]-NH2 into the subZI significantly increase T IBAT, whereas and the MC4-R antagonist, HSO24 significantly decreases T IBAT alone and if pre-injected into the subZI before the MC4-R agonist, blocks the agonist-induced increase in T IBAT.

BAT also has sensory innervation, as revealed by injection of the anterograde H129 strain of herpes simplex 1 virus, a transneuronal sensory nerve tract tracer, into the tissue with infected neurons appearing across the neuroaxis. Injection of both H129 to label central sensory circuits and PRV to label SNS outflow into the same IBAT pad results in doubly-infected neurons (SNS-sensory neural loops) in several brain areas including the PVH suggesting neural feedback regulation of the SNS drive to BAT. Local IBAT injection of capsaicin to ablate small-unmyelinated sensory nerves impairs T IBAT responses to acute cold exposure, suggesting BAT sensory nerves help control its thermogenic function.

SP 8.4

Brown fat activation by cold and insulin. Virtanen KA, Turku PET Centre – University of Turku and Turku University Hospital.

Background/Aims: The role of brown adipose tissue (BAT) in human metabolism has been recently challenged by the findings that BAT is functionally...
active in healthy adults. Interestingly enough little has known about the normal physiology of BAT in humans. Our aim in Turku PET Centre is to study the normal physiology of human BAT in health availing to contrast that with the changes found for example in obesity.

Methods: We have studied normal weighed (n=27) subjects during acute cold exposure, during insulin stimulation and after overnight fasting (= control). Glucose uptake (GU) and perfusion in BAT, subcutaneous adipose tissue (WAT) and skeletal muscle can be measured in vivo using 15O-H2O- and 18F-FDG-PET/CT. Energy expenditure with indirect calorimetry can be assessed simultaneously during PET/CT studies.

Results: Majority (70%) of the normal weighed subjects have BAT activation during cold exposure. During cold exposure, mean BAT GU increases 10-fold (9.1±5.1 vs. 0.9±0.4 umol/100g/min, P=0.002) and perfusion is doubled (15.9±4.9 vs. 7.5±3.7 ml/100g/min, P<0.001) to control in normal weighed adults. BAT perfusion and GU correlate in a curvilinear fashion (r=0.82, P<0.001) in cold. During insulin stimulation, mean BAT GU is 5-fold (4.7±2.4 umol/100g/min, P<0.001) to control and close to skeletal muscle GU (6.0±2.5 umol/100g/min) while insulin-stimulated increment in WAT GU is about 150%. No association is found between insulin-stimulated BAT GU and perfusion or whole-body insulin sensitivity. Plasma norepinephrine concentration increases substantially during cold exposure and energy expenditure tends to be higher among the subjects with active BAT.

Conclusion: Both GU and perfusion in human BAT are increased in response to cold, indicating active thermogenesis. Insulin stimulates GU in BAT significantly and independently of its perfusion, suggesting the metabolic role of BAT also during the insulin stimulation.

Keywords: BAT, cold, insulin, FDG-PET/CT, perfusion

SP8.5
Implications of the thermoneutral zone for studies on human brown adipose tissue. Kingma BRM1, van Marken Lichtenbelt WD NUTRIM School for Nutrition, Toxicology and Metabolism of Maastricht University Medical Center - Human Biology

Background: The thermoneutral zone is defined as the range of ambient temperatures without regulatory changes in metabolic heat production or evaporative heat loss. Many factors influence the thermoneutral zone, such as body composition, clothing, energy expenditure, age and gender. These factors have the potential to introduce bias in study results and therefore need to be taken into consideration in many metabolic studies. Aim: The aim of this presentation is to 1) provide insight in how the human TNZ is affected by internal (body) and external (environmental) factors, 2) indicate how skin blood flow characteristics could be used as an objective criterion for determining whether someone is in the thermoneutral zone, 3) explain implications of taking the TNZ into account in metabolic studies on human brown adipose tissue.

Key words: Thermoregulation, Brown Adipose Tissue, Ageing, Thermoneutral Zone
PT.01
Modern theory of thermoregulation and its application to practice. Ivanov KP Pavlov Institute of Physiology, Russian Academy of Sciences – Thermoregulation and Bioenergetics

After prolonged and fruitful studies of thermoregulation the researchers concluded that the effective thermoregulation in fact occurs only in the comfort zone. In the thermal comfort zone the thermal sensitivity of an organism is aggravated and the sensitivity of temperature regulation in the human hypothalamus attains 0.1-0.05°C. In these cases of thermoregulation the heat content of the body seems to play a certain role. It is calculated by an organism in a complicated manner from the temperature of hypothalamus and the temperature of various sites of the skin.

At a normal comfort temperature or in the regions close to the comfort temperature without physical work a man regulates the body temperature with a great accuracy. Under a strong cooling influence of the environment the regulation changes. A strong counteraction to cooling arises – the cold shivering. This is an emergency reaction. It cannot last for a long time. A man protects himself against such strong cold actions either by warm clothes or warm shelter. The animals protect themselves against strong cold by their external heat insulating covers or, like humans, by warm shelters. No other thermoregulation mechanisms protecting against strong cold exist in man and in animals.

A man has only one sufficiently strong counteraction to the action of high and very high environmental temperature – this is diaphoresis. A comparatively weak diaphoresis can last for a long time. A strong diaphoresis disrupts the water and ion exchange in an organism and, therefore, cannot last long. In this case to avoid death a man must find any cooling effects (water, wind, etc.).

The level of metabolism was fixed for millions of years. It exists as the most important biological constant. The attempts to increase the metabolism for protection against cold or decrease it for protection against overheating by pharmacological Methods are doomed to failure. There are almost no corresponding remedies. Adaptation to cold or heat in man and animals is never associated with a prolonged increase or decrease in the body temperature. Only a reinforced heat insulation of the body upon adaptation to cold or an enhanced heat loss upon adaptation to heat are capable of preserving life and temperature homeostasis in man and animals.

Nowadays thermoregulation is studied in sufficient details. In humans it exists only for the body temperature corrections in the zone of temperature comfort. Upon strong temperature actions the thermoregulation reactions are rather weak and cannot provide for a stable and prolonged adaptation to cold or heat without disrupting the physiological state of an organism.

PT.02
Effect of TRPM8 activation on thermoregulatory and immune response at cooling and heating. Kozyreva TV, Kozaruk VP, Eliseeva LS, Tkachenko EYa, Russian Academy of Medical Sciences – Physiology – Thermophysiology

Results of recent studies indicate that temperature-sensitive ion channels, such as TRP channels are in the basis of thermoreception, but their possible role in maintenance of body functions is not clear. In the present work we studied, how a preliminary activation of TRPM8 ion channel by its agonist menthol influences on thermoregulatory and immune parameters in thermoneutral conditions and under cold and heat exposure.

In thermoneutral conditions activation of TRPM8 ion channel: 1) increased oxygen consumption and decreased respiratory exchange ratio, which may be evidence of enhanced fat oxidation; 2) enhanced the antigen binding and inhibited the antibody production in the spleen, significantly reduced the amount of IgG in blood.

At deep cooling (rapid and slow) on the background of activated TRPM8 ion channel there were: 1) the decrease in temperature thresholds for all cold-defense responses; 2) the enhancement of metabolic component of emergency thermogenesis at rapid cooling, and the increase in the skin blood vessel constrictor response at slow cooling. All these lead to improved maintenance of core temperature in the cold.

For the immune parameters, preliminary activation of TRPM8 eliminated the inhibitory effect of deep cooling on antigen binding and antibody production in spleen.

At heating, the activation of TRPM8 caused: 1) a decrease in temperature thresholds for heat-defense skin blood vessel response; 2) earlier increase in metabolic response; 3) elimination of inhibitory effect of heating on antibody production; and 4) stimulation of the antigen binding in spleen due to heating inverted to suppression at heating on the background of TRPM8 activation.

Thus, the activation of TRPM8 ion channel may significantly change the functional responses of thermoregulatory and immune systems confirming their interrelation. The comparison with the situation of TRPV1 activation can be analyzed.

Keywords: TRPM8, thermoregulation, immune response, cooling, heating.
PT.03
Comparison of the effects of ATP and noradrenaline on thermoregulatory responses to cooling. Meyta ES, Kozyreva TV, Russian Academy of Medical Sciences – Institute of Physiology – Thermophysiology
It is well known that sympathetic nervous system participates in body response to cold. Mostly the thermoregulatory responses to cold were thought to be related to its main mediator noradrenaline. Recently it is established that co-mediators of noradrenaline are also ATP (adenosinetriphosphate) and neuropeptide Y. The aim of this study was to find out how the application of ATP influences on the thermoregulatory parameters in thermoneutral conditions and under cold exposure and compare it with the effects of noradrenaline.
In the experiments in rats it was shown that ATP in thermoneural conditions causes an increase in total metabolism which is accompanied by decrease in the respiratory exchange ratio. The last means that ATP makes for the prevalent use of lipids as the main energetic substrate. In the cold ATP promotes a decrease in temperature thresholds for thermoregulatory responses and increase in the value of metabolic response mostly due to shivering thermogenesis.
Comparison of the effects of two co-mediators of sympathetic nervous system - ATP and noradrenaline on thermoregulatory parameters shows that they strengthen the different components of thermoregulatory response to cold. According to our and other investigators previous works noradrenaline mostly increases nonshivering thermogenesis and the skin blood vessel constriction (decrease in heat loss) but ATP mostly increases the shivering thermogenesis.
Keywords: ATP, noradrenaline, thermoregulation, cold.

PT.04
Carbon monoxide downmodulates the locus coeruleus nitric oxide pathway during fever. Soriano RN¹, Kwiatkowsk M², Battalhão ME², Branco LGS³, Carnio EC³, EERP-USP – Fisiologia, ²EERP-USP – Fisiologia, ³FMRP-USP – Fisiologia
Background/Aims: Locus coeruleus (LC) carbon monoxide (CO) is anti-pyretic whereas LC nitric oxide (NO) is propyretic. Aiming at further exploring the mechanisms underlying their anti- and propyretic properties, we investigated the putative interplay between these neuromodulators in the LC. Methods: Male Wistar rats (300-340 g) were implanted with a guide cannula toward the fourth ventricle (4V) and a temperature datalogger capsule in the peritoneal cavity (to record Tb). Animals were microinjected with a CBS inhibitor (AOAA 200 pmol/µg) or saline (2 µl) and exposed to normoxia or hypoxia (7%, for 1 hour).
Results: Under normoxia, AOAA intra-POA had no effect on Tb: AOAA 11.07 ± 8.25 vs. saline 4.69 ± 10.23°C.min. Under hypoxia, AOAA significantly attenuated anapyrexia: AOAA -37.16 ± 11.17 vs. saline -77.92 ± 8.26°C.min. Additionally, animals were microinjected intracerebroventricularly with AOAA (200 pmol) or saline (2 µl) and exposed to normoxia or hypoxia for 1h. Hypoxia caused an increase in AV3V hypoxia-induced anapyrexia.
Keywords: Gaseous neuromodulator, AOAA, Body temperature, H2S, Hypothalamus
Financial Support: CAPES, FAPESP, CNPQ.

PT.05
Hydrogen sulfide as a cryogenic mediator of hypoxia-induced anapyrexia. Kwiatkoski M¹, Soriano RN², Branco LGS³, EERP-USP – Fisiologia, FMRP-USP – Fisiologia
Background/Aims: The roles played by nitric oxide (NO) and other neurotransmitters have been documented during hypoxia-induced anapyrexia, but no information exists with respect to the cystathionine β-synthase (CBS)-hydrogen sulfide (H2S) pathway. Methods: Male Wistar rats (270-300g) were implanted with a guide cannula toward the preoptic area (POA) and with a temperature datalogger capsule in the peritoneal cavity (to record Tb). Animals were microinjected with a CBS inhibitor (AOAA 200 pmol/2 µl) or saline (2 µl) and exposed to normoxia or hypoxia (7%, for 1 hour).
Results: Under normoxia, AOAA intra-POA had no effect on Tb: AOAA 11.07 ± 8.25 vs. saline 4.69 ± 10.23°C.min. Under hypoxia, AOAA significantly attenuated anapyrexia: AOAA -37.16 ± 11.17 vs. saline -77.92 ± 8.26°C.min. Additionally, animals were microinjected intracerebroventricularly with AOAA (200 pmol) or saline (2 µl) and exposed to normoxia or hypoxia for 1h. Hypoxia caused an increase in AV3V hypoxia-induced anapyrexia.
Keywords: Hydrogen sulfide, POA, hypoxia, anapyrexia.
Financial Support: FAPESP, CNPQ, CAPES.

PT.06
Expression of thermosensitive TRP ion channel genes in hypothalamus of normal and cold adapted rats. Voronova IP, Tuzhikova AA, Kozyreva TV Russian Academy of Medical Sciences – Physiology – Thermophysiology

Results: In febrile rats, microinjection of ZnDPBG reduced LC bilirubin (0.227 ± 0.032 vs. 0.100 ± 0.022 mg of bilirubin/mg of protein) and increased LC NOx (225.26 ± 26.49 vs. 395.69 ± 44.61 pmol of NOx/mg of protein), whereas L-NMMA diminished LC NOx (225.26 ± 26.49 vs. 71.77 ± 16.18) and reduced LC bilirubin (0.227 ± 0.032 vs. 0.112 ± 0.029); furthermore, NOC12 augmented LC bilirubin (0.227 ± 0.032 vs. 0.261 ± 0.036), whereas CORM-2 diminished LC NOx (225.26 ± 26.49 vs.103.75 ± 27.04).
Conclusion: The LC HO/CO pathway downmodulates LC NOS activity whereas the LC NOS/NO pathway upmodulates LC HO activity during fever.
Keywords: bilirubin; hemeoxygenase; nitric oxide synthase; lipopolysaccharide; gaseous neuromodulator.
It is known that the characteristics of the hypothalamic temperature-sensitive neurons change after long-term adaptation to cold. One of the possible molecular mechanisms of the adaptive modifications can be changes in the gene expression of recently identified temperature-sensitive TRP ion channels.

The purpose of this study was to find out if there are the expression of all known temperature-sensitive TRP ion channels in the hypothalamus of rats and how the long-term adaptation to cold influences on the expression of these genes. Experiments were carried out on Wistar rats. Control rats were kept at 20-22°C, cold adapted – 5 weeks at +5°C. The expression of TRP ion channel genes was assayed by quantitative RT-PCR.

It was found that expression of genes of TRP ion channels activating at temperature above 30°C – TRPV1, TRPV2, TRPV3, TRPV4 was pronounced, while the expression of TRP ion channels activating at lower temperature – TRPA1, TRPM8 was negligible. This is consistent with electrophysiological studies showing the prevalence of warm-sensitive neurons in hypothalamus.

The expression of gene of TRPV3 ion channel activating in physiological range of temperature (31-39°C) changed after long-term adaptation to cold: the level of its mRNA was 1.5-fold decreased in comparison with control. This is in agreement with our previous data on decreasing after adaptation to cold the portion of warm-sensitive neurons which are sensitive in this range of temperature (Kozyreva, Pierau, 1994).

Thus, obtained results support the idea that changes in the TRP channel genes may be in the basis of molecular mechanisms of changes in the hypothalamic neuron thermosensitivity during long-term thermal effects.

The work is supported by Russian Foundation for Basic Research, grant No 12-04-00401-a.

PT.08
Hypoxia-induced anapyrexia is influenced by light-dark cycle. Scarpellini CS¹, Gargaglioni LH², Bicego KC² 1IB – Fisiologia, 2FCAV-UNESP – Morfologia e Fisiologia Animal, Background/Aims: Hypoxia induces a regulated decrease in body temperature (Tb) by increasing heat loss (HL) and reducing O2 consumption (VO₂), a phenomenon named anapyrexia. No data exist regarding this response in different phases of day. Our preliminary data in rats indicates bigger amplitude in Tb reduction during hypoxia at the beginning of dark than at the beginning of light phase. Considering there is a circadian oscillation of Tb, VO₂ and HL, we investigated the influence of basal VO₂ and HL on the amplitude of hypoxic anapyrexia in two phases of day.

Methods: Body temperature, VO₂ and HL index were determined in unanesthetized male Wistar rats (260-310g BW) before and during 1hour of 7% O₂ exposure at two different times: 1h after the beginning of light or dark phase. Animals were kept at 26°C.

Results: The normoxic Tb of all animals was similar (light phase: 36.8 ± 0.24 °C; dark phase: 36.9 ± 0.1°C), despite VO₂ was higher at night (18.7 ± 0.85 vs 22.4 ± 0.9 mLO₂/kg⁻¹.min). Hypoxia reduced Tb (p<0.0001) and VO₂ (p< 0.01) in both groups, responses that were more pronounced at night. No significant difference was observed in HL index among groups.

Conclusion: The more prominent Tb reduction during hypoxia at the beginning of dark phase seems to be due, at least in part, to inhibition of thermogenesis, which is higher in this phase of day. Key words: Temperature, phase of day, oxygen consumption, heat loss, circadian cycle

PT.09
Influence of il6st gene on thermoregulation and blood level of Interleukine-6. Khramova GM¹, Voronova IP², Kulikov AV², Kozyreva TV¹ 1Russian Academy of Medical Sciences – Physiology – Thermophysiology,
There is evidence of change in the level of interleukin-6 (IL-6) in the blood under different temperature conditions. The effects of IL-6 are realized via a receptor, which transducer unit gp130 is encoded by the gene il6st.

Methods

Background and Aim: Endogenous opioids (mu, kappa and delta) in brain are involved in the development of febrile response to endotoxin, but no conclusive data exist about the role of these receptors in the increase of body temperature (Tb) induced by restraint stress. Bicego KC, Butler L, Scarpellini CS, Gargaglioni LH. FCAV-UNESP – Morfologia e Fisiologia Animal, 1IB-USP

Methods: Body temperature of unanesthetized adult male Wistar rats (245–260g BW) was measured by intra-abdominal datalogger before and after intracerebroventricular (icv) microinjection of CTAP in restrained (40 min) and unrestrained animals.

Results: Under control condition, saline, CTAP, Nor-BNI and Naltrindole had no effect on Tb. Restraint stress caused increase in Tb of all groups (from 36.9 ± 0.1 to 38.1± 0.1°C; p< 0.0001), a response that was inhibited by CTAP (10mg; p< 0.01), Nor-BNI (1.0 and 5.0mg; p< 0.05) and Naltrindole (12.5mg; p< 0.01).

Conclusion: These results indicate that endogenous opioids acting on mu, kappa and delta receptor in the central nervous system are involved in the development of restraint-induced fever, but they seem to not participate in tonic control of Tb during euthermia. Financial Support: FAPESP, CNPq, INCT Fisiologia Comparada.

Keywords: Body temperature, stress, Nor-BNI, CTAP, Naltrindole

PT.11

Meth-induced hyperthermia is a multi-phase phenomenon resulting from serial and overlapping actions on different anatomical sites. Sanchez-Alavez M, Conti B, Zhurkov V, Wood M, Fox HS, Bartfai T, Marcondes MC. The Scripps Research Institute – Molecular and Integrative Neurosciences, 2University of Nebraska Medical Center – Pharmacology and Experimental Neurosciences

Methamphetamine abuse induces hyperthermia, a condition that contributes to neurotoxicity, induces multi-organ failure, and is frequently the cause of Meth-associated mortality. We have characterized the different phases of hyperthermia following Meth injection in mice. We have shown that hyperthermia is a complex phenomenon partially regulated by different central and peripheral pathways. We have dissected the contribution of different compartments to thermogenesis and locomotor activity-associated heat production to the different phases of Meth induced hyperthermia. These compartments are 1) a pre-optical area of the hypothalamus (POA)-driven brown adipose tissue (BAT) thermogenesis identified as a partially responsible for the first acute peak, 2) POA-derived thermogenesis responsible for a steady long lasting temperature elevation, and 2) the muscle thermogenesis, which is partially responsible for a second wave of more aggressive increment of temperature following Meth.

The muscle contribution to hyperthermia overlaps but differs from POA-mediated temperature elevation. The use of Ca++ channel blockers was not enough to decrease the secondary peak, which in humans is the most life-threatening phase of hyperthermia. However, BAT ablation decreased temperature by 1oC, suggesting an additive thermogenic effect of BAT, where sympathetic-dependent mitochondrial activation may contribute to the phenomenon. Thus compartmentalized actions in POA-driven BAT activation, POA and muscles differ in quality and kinetics, causing a distinctive relative contribution of these components to hyperthermia in Methamphetamine abuse.

PT.12

Heat acclimation increases hypoxia-inducible factor 1alpha expression but not erythropoietin and vascular endothelial growth factor in athletes. Shin YO, Kim TW, Han MK, Lee JB, Min YK, Yang HM.
Exposed to a thermoneutral baseline 0.5 h (T_air=30.1°C), and 12 elderly. Supine subjects (0.04 Clo) were % body fat (DXA) were measured in 12 young adults skin and core temperatures (iButtons, CoreTemp), and mitochondrial uncoupling. However, reduced amounts of mitochondria still do not explain why energy expenditure decreased in elderly. This observation may be explained by temperature-induced changes on metabolic rates of tissues, also known as Arrhenius’ law or the Q_10-effect. A 1°C drop in limb muscle tissue temperature can already explain the decreased energy expenditure. Moreover, the Q_10-effect also holds for peripheral tissues in young adults. Therefore, in young adults some of the NST may be obscured by decreased thermogenesis in cooled peripheral tissues. 

Keywords: Thermoregulation, Non-Shivering Thermogenesis, Ageing

PT. 14
The effect of regional thermal sensation on entire body thermal sensation. Fukagawa K Hiroshima International University – Socioenvironmental Design

In recent years, global warming is becoming a serious problem. In addition, according to the devastation happened on March 11, 2011 in Japan, country’s energy policy is facing a turning point to establish a less harmful and less energy based society.

Heat island itself is considered as human disaster mainly caused by the increase of the exhaust heat relating to the energy consumption increase. More focusing on the energy consumption, air conditioning dominates the large ratio of the energy consumption. For that reason, to decrease the energy consumption, amelioration of the air conditioning system is necessary. For the amelioration of the air conditioning system, floor heating and cooling system is one of the answers since this system directly warms and cools the human body. There are several studies focusing on this system.

Kurazumi et al. have had several researches on the floor cooling system based on the human body posture. However, to efficiently utilize the floor heating and cooling system, analysis of the effect of regional thermal sensation on entire body sensation is required. For that reason, the purpose of this research is to clarify the above mentioned effect to design more energy saving heating and cooling system.

PT. 15
Activation of (non-)nitrergic hypothalamic MnPO neurons due to systemic thermal and osmoregulatory stimulations in the rat. Gerstberger R, Ott D, Marks D, Weber T, Roth J Justus-Liebig-University Giessen – Veterinary Physiology and Biochemistry

Background/Aims: The median preoptic nucleus (MnPO) receives afferent signals from (extra-)hypothalamic neuroglial structures coding changes in tonicity/volume of the extracellular fluid (ECF) compartment or the animal’s thermal status. Efferent projections of MnPO neurons to the parvocellularparaventricular nucleus (pPVN) lead to final signal integration of both homeostatic control loops. MnPO-intrinsic nitric oxide (NO) formed by neuronal NO synthase (nNOS) acts as prime neuromodulatory candidate underlying hypothalamic control of body temperature and ECF homeostasis. The aim of the study was to clarify whether (non-)nitrergic MnPO neurons projecting to the pPVN are
responsive to systemic thermal, osmotic and volume stimulations in the adult conscious rat.

Methods: Stereotaxic microapplication of True-Blue into the pPVN was used for retrograde neuronal tracing of projecting MnPO neurons. Core temperature, locomotor activity and water intake were telemetrically recorded in euvhydrated animals (EUH), and animals subjected to 24 hrs water-deprivation (DEH), 48 hrs exposure to 30°C (HEAT) or polyethylene glycol induced hypovolemia (PEG). In coronal brain sections, immunohistochemistry for nNOS and Fos was combined with the analysis of True-Blue positive neurons to quantify the number of activated (non-)nitrergic neurons projecting to the pPVN. Functional activation of (non-)nitrergicMnPO neurons was evaluated employing a primary Fura-2 loaded MnPO cell culture system and stimulation of MnPO neurons with angiotensin II (AngII), norepinephrine respectively glutamate as important neurmodulators relaying changes in ECF toxicity, volume respectively body temperature to MnPO neurons. Results: Telemetric data combined with blood analysis allowed to define DEH, HEAT and PEG treatments as rather pure osmotic, thermal and volume stimuli. All stimuli evoked significant nuclear Fos translocation in MnPO neurons, however with differential pattern formation. Osmotic and volume, but not thermal stimuli, led to marked activation of MnPO-intrinsic nitrergic neurons (10-25 %), indicative of NO being involved in MnPO mediated perception of afferent osmoregulatory signals, and 15-20 % of these activated nitrergic neurons projected efferently to the pPVN. Functional data obtained in a primary MnPO cell culture system using the intracellular calcium imaging technique demonstrated activation of nitrergic neurons exclusively by AngII, a known peptidergic neurmodulator of osmosensitivubornical organ neurons outside the blood-brain barrier, efferently innervating MnPO intrinsic neurons. Conclusion: The transmitter-coding of thermostresponsiveMnPO neurons relaying information to the pPVN still remains to be elucidated. Keywords: Median preoptic nucleus, retrograde neuronal tracing, thermo- and osmoreponsive neurons, transmitter coding, calcium imaging

PT.16

Age-dependent decline of hypothalamic neurogenesis and of heat tolerance in long-term heat-acclimated rats. Matsuzaki K, Katakura M, Hara T, Hashimoto M, Shido O Shimane University – Medicine

Background/Aims: It was previously reported that constant exposure to moderate heat facilitates progenitor cell proliferation and neuronal differentiation in the hypothalamus of rats. The present study investigated age-dependent changes of heat exposure-induced hypothalamic neurogenesis and of heat tolerance in rats. Methods: Male Wistar rats, 5 weeks (Young), 10-11 months (Adult) or 22-25 months (Old), were subjected to an ambient temperature (Ta) of 32°C for 40-50 days (long-term heat-exposed rats, LT), while control rats (CN) were constantly kept at a Ta of 24°C. Bromodeoxyuridine (BrdU) was intraperitoneally injected daily for 5 consecutive days (50 mg/kg/day) after commencing heat exposure. After the end of heat exposure period, all rats were kept at a Ta of 24°C for 48 h, and subjected to heat tolerance test, i.e. they were exposed a Ta of 36°C for 3 h. After the test, brain was removed for immunohistochemical analysis. Results: In LT, the magnitudes of rises in abdominal temperature (Taab) of Young, Adult and Old during heat tolerance test were significantly smaller than that of respective CNs, suggesting that heat acclimation improved heat tolerance. The amount of increase in Taab in LT became greater with advancing age. Immunohistochemical analysis showed that in Young, the number of hypothalamic BrdU-immunopositive (BrdU+) cells of LT was significantly larger than that of its CN. However, heat exposure did not affect the number of BrdU+ cells in the hypothalamus of Adult and Old. Conclusion: Aging may interfere with heat exposure-induced hypothalamic neurogenesis and with improvement of heat tolerance following long-term heat acclimation. Keywords: Aging, heat acclimation, BrdU, hypothalamus, rats

PT.17


It remains unclear whether heat intolerance is associated with an impaired or enhanced stress response. We hypothesized that heat exposure causes a greater stress response in heat-intolerant (INT) than heat-tolerant (TOL) mice. Thirty-eight mice were tested twice (7 day interval) in an environmental chamber (39.5°C) to assess tolerance to heat. Subsequently the mice were assigned into tolerant (TOL), moderately tolerant (MT) and intolerant (INT) groups based on their thermal responses to heat exposure. Real-time core temperature (Tc), blood pressure, and heart rate were recorded by telemetry during heat exposure. Tissue samples were collected following the second heat exposure. Ten sham-implanted mice were not exposed to heat as controls. INT mice had significantly higher peak mean arterial pressure and heart rate than TOL mice during heat exposure. Plasma corticosterone levels were significantly higher in INT than control mice, but not higher than TOL or MT mice. No changes in plasma cytokines or makers of oxidative stress were found across the four groups. All heat-exposed mice showed an increase in heat shock protein 72 (HSP72) in the kidney, whilst the INT mice had the highest concentration. INT mice also showed significant increases in HSP72 in all other tested organs/tissues including liver, heart and soleus and gastrocnemius muscles. These Results suggest that heat exposure causes an extensive stress response in animals with heat intolerance. The kidney seems to be more sensitive to heat exposure than other organs/tissues, suggesting it may be more vulnerable to heat injury. (supported by USUHS R091EH and ONR N0001411MP20025)
PT.18
Assessing vasomotor dysfunction to investigate peripheral neuropathy. Wu Y¹, Nieuwenhoff MD², Huygen FJPM², Van der Helm FCT¹, Niehof S², Schouten AC¹ ¹Delft University of Technology – Biomechanical Engineering, ²Erasmus Medical Center – Anesthesiology

Background: Approximately 2% of the population suffers from small nerve fiber neuropathy, primarily as a result of diabetes. Skin biopsy, the current gold standard for diagnosing small nerve fiber neuropathy, is invasive, labor-intensive and has limited accuracy. There is a clinical demand for a method that enables quantitative diagnosis of small nerve fiber neuropathy non-invasively. Method: Small nerve fibers are known to affect the local vasomotion of the skin. In this project we investigate vasomotion by applying local thermal stimuli to the skin with an irradiation heat source. The response to the thermal stimuli is evaluated based on three signals: 1) thermodynamic response of the skin, recorded with thermography, 2) blood flow, measured with laser Doppler flowmetry and 3) arterial compliance, assessed with pulse transit time. Results: 1. After thermal stimuli skin temperature decreases in an (approximately) exponential curve. The time constant of a curve is affected by the tissue beneath the skin. For example, the time constant on a superficial vein is lower than that on a muscle. 2. The blood flow changes differently when the skin is heated up to different temperatures. The Results imply that more than one thermoregulatory mechanism is involved in response to thermal stimuli. Conclusion: Pilot experiments on healthy subjects demonstrate that the method is promising and that clues about thermoregulation as well as thermodynamic properties of human tissue can be obtained. In the next years we will optimize the methodology and investigate the potential in diabetes patients. Keywords: Small nerve fiber neuropathy, vasomotion, skin temperature, blood flow, pulse transit time

PT.19
Social defeat stress-induced hyperthermia involves brown adipose tissue thermogenesis mediated by medullary raphe sympathetic premotor neurons. Nakamura K¹, Lkhagvasuren B², Kataoka N¹, Nakamura Y¹, Oka T² - ¹Kyoto University – Career-Path Promotion Unit for Young Life Scientists, ²Kyushu University – Psychosomatic Medicine

Psychological stress-induced hyperthermia is a fundamental autonomic response in mammals. However, it is controversial whether this stress response involves sympathetic thermogenesis in brown adipose tissue (BAT). To test this possibility, here, we examined the effect of systemic blockade of β₃-adrenoceptors, a major adrenoceptor subtype mediating BAT thermogenesis, on hyperthermic response evoked by social defeat stress, a psychological stress model. Intruder rats that were defeated by a dominant resident conspecific exhibited a rapid increase in abdominal temperature by up to 2.0°C. Prior injection (i.p.) of the β₃-adrenoceptor antagonist, SR59230A into the intruder rats attenuated the stress-induced hyperthermia. Direct measurement of BAT temperature using a telemetry system detected immediate elevation of the temperature in response to the psychological stress. We further examined activation of medullary raphe neurons expressing vesicular glutamate transporter 3 (VGLUT3), which are known as sympathetic premotor neurons controlling BAT thermogenesis for cold defense and fever. These VGLUT3-expressing neurons exhibited expression of Fos, a marker of neuronal activation, in response to exposure to social defeat stress. These Results indicate that psychological stress-induced hyperthermia involves BAT thermogenesis through activation of VGLUT3-expressing medullary raphe sympathetic premotor neurons.

PT.20
Comparative thermoregulatory physiology and behavior of blue and black wildebeest. Lease HM, van Staden A, Fuller A, Hetem RS University of the Witwatersrand – Physiology

Background/Aims: Understanding the physiological and behavioral strategies that enable animals to survive in different thermal environments is important for understanding which factors constrain biodiversity in ecological systems. Blue and black wildebeest currently co-exist in several locations in South Africa, though may have different thermoregulatory strategies allowing them to inhabit separate niches within these locations. Blue and black wildebeest have the potential to interbreed when not ecologically separated, but whether their thermal differences are significant enough to prevent hybridization when they are artificially confined to the same geographic location is unknown. In this study we establish and compare the daily and seasonal patterns of body temperature and the behavioral mechanisms of thermoregulation in free-ranging black and blue wildebeest. Methods: We implanted miniature temperature and activity data loggers in blue and black wildebeest that co-exist in Mokala National Park (South Africa). We will use this data in conjunction with microclimate measurements and field observations to assess wildebeest core body temperature, vasomotor control, locomotor activity, microclimate selection, body position with respect to the sun, and habitat selection. Results/Conclusions: Here we present preliminary data on the thermal and activity patterns of wildebeest. We assess the effect of ambient temperature on wildebeest activity and core body temperature, and compare these effects during winter versus summer, for both species. Results suggest that wildebeest are good homeotherms, and that both blue and black wildebeest utilize behavioral mechanisms for thermoregulation. Blue wildebeest, however, spend a higher proportion of time shade-seeking, and do so at lower ambient temperatures, than black wildebeest.

PT.21
Adaptive modification of hormones related with thermoregulation after short-term heat acclimation in athletes Shin YO¹, Kim TW², Lee JB³ ¹Soonchunhyang
University – Health Care, Graduate School, 
\textsuperscript{2}Soochunhyang University – Health Care, 
\textsuperscript{3}Soochunhyang University – Physiology.

Chronic exposure to environmental heat improves tolerance via heat acclimation. Heat acclimation attenuated metabolic rate because thermogenesis is less important in high ambient temperature. Thyroid hormones have long been known to be involved in the control of thermoregulation. However, it is equivocal that always thyroid hormones may contribute to the promotion of energy metabolism. Thus, we examined that always thyroid hormones may contribute to the control of thermoregulation. However, it is equivocal that always thyroid hormones may contribute to the promotion of energy metabolism. Thus, we examined whether heat acclimation affects thyroxine and other hormones related with energy metabolism; prolactin, 17β-estradiol, and insulin in athletes. Nine subjects who were male college tennis athletes participated in repeated half-body immersion (43°C) for 3 weeks. During the 30 min intermittent half-body immersion, subjects took short 60-90 sec break 3 times at 5, 10, 20 min. Before and after 3 week experiment, blood samples were taken from antecubital vein and body temperatures were measured at rest. Serum protein levels of thyroxine, prolactin, 17β-estradiol, and insulin were analyzed by commercial ELISA kit. After repeated hot water immersion, resting level of thyroxine increased. On the contrary, those of prolactin, 17β-estradiol, and insulin decreased. There were no significant alterations of skin and mean body temperature. Our Results show that heat acclimation modifies resting levels of metabolic thermoregulative hormones, which is possibly involved in the metabolic thermosuppression. However, thyroxine seems not to be an essential factor in the control of thermoregulation in heat-acclimated process.

**PT.22**

Limb regeneration stabilizes thermoregulatory preference in the red-spotted newt (\textit{Notophthalmus viridescens}). Tattersall GJ, Tyson TM, Lenchyshyn JR, Carlone RL Brock University – Biological Sciences.

Red-spotted newts (\textit{Notophthalmus viridescens}) are capable of re-growing limbs, tails, jaws, spinal cords, as well as parts of the eye. As small ectotherms that are aquatic as adults, they naturally conform to the temperature of their surrounding water. Environmental temperatures, however, can alter the red-spotted newts’ metabolic processes, including their rate of tissue regeneration; whether an optimal temperature for this rate of regeneration exists is unknown. However, newts do exhibit behavioral preferences for certain temperatures, and these thermal preferences are known to vary with season and thermal acclimation. Given their flexibility in behavioral thermoregulation and the temperature sensitivity of metabolism and growth, we hypothesized that the process of tissue regeneration would also affect thermal preference. We predicted that regenerating newts would select environmental temperatures which maximized the rate and effectiveness of regeneration. Thermal preference trials revealed that regenerating newts consistently selected temperatures of $\approx 25°C$, coincident with the temperature that produced highest survival. This temperature selection was warmer than that of uninjured conspecifics, but was lower than the temperature which maximized the rate of regeneration. Interestingly, regenerating newts maintained a more stable temperature preference than sham newts that exhibiting temporal changes in thermal preference, suggesting that precision in thermoregulation may be more important to regenerating individuals, than to non-injured individuals.

**PT.23**

Endogenous hydrogen sulfide mediates LPS-induced fever in rats. Kwiatkoski M\textsuperscript{1}, Araújo R\textsuperscript{2}, Azevedo L\textsuperscript{2}, Carnio EC\textsuperscript{3}, Soriano RN\textsuperscript{3}, Branco LGS\textsuperscript{2}. 1FMRP-USP – Fisiologia, 2FMRP-USP – Morfologia, Estomatologia e Fisiologia, 3USP – Enfermagem Geral e Especializada.

Inhibition of peripheral hydrogen sulfide synthesis modulates endotoxic fever. Soriano RN\textsuperscript{1}, Cunha JS\textsuperscript{1}, Batalhão ME\textsuperscript{1}, Kwiatkoski M\textsuperscript{1}, Branco LGS\textsuperscript{2}, Carnio EC\textsuperscript{3}. 1USP – Enfermagem Geral Especializada, 2FMRP – Fisiologia, 3FMRP – Morfologia, Estomatologia e Fisiologia.

**Background/Aims:** Hydrogen sulfide (H2S), a gaseous molecule endogenously produced by the enzyme CSE, has been documented to act as a potent modulator of systemic inflammation. We aimed at investigating whether H2S modulates LPS-induced fever in rats. 

**Methods:** Male Wistar rats (270-300g) were implanted with a guide cannula toward the third ventricle (for intracerebroventricular microinjection) and with a temperature datalogger capsule in the peritoneal cavity (to record Tb). Animals were microinjected with a CBS inhibitor (AOAA, 100 pmol/2 μl), H2S donor (Na2S, 260 nmol/2 μl) or saline (2 μl) and injected with LPS (100 μg/kg; ip). 

**Results:** LPS combined with saline caused a typical rise in Tb (from 36.96°C to 38.10°C, about 2 hours after injection). When LPS was combined with AOAA we observed a further increase in Tb of about 2.41°C. Conversely, microinjection of Na2S significantly attenuated febrile response (rise of about 0.61°C). 

**Conclusion:** The present Results are consistent with the notion that endogenous H2S plays an important antipyretic role in LPS fever in rats. 

**Keywords:** Gaseous neuromodulator, AOAA; Body temperature; H2S; Na2S. 

**Financial Support:** CAPES, FAPESP and CNPQ.
Contribution of the dopamine receptor 1 (D1R) within the paraventricular nucleus in the heat stress-induced cardiovascular and thermoregulatory adjustments. Guimarães JB1, Leite LHR2, Zheng, H3, Coimbra CC1, Patel KP4, UFMG – Fisiologia e Biofísica, 2UFJF – Fisiologia, 3University of Nebraska Medical Center – Cellular and Integrative Physiology, 4University of Nebraska Medical Center – Physiology

Results: Injection of PAG caused no significant change in Tb of euthermic animals, e.g., those injected with saline instead of LPS (277.9 ± 12.36 vs. saline 315.1 ± 29.54°C×min; P = 0.2436; n = 8-9 per group). Injection of LPS combined with saline (control of PAG) evoked a typical rise (of 1.6°C) in Tb, i.e., LPS-induced fever (from 36.52 ± 0.20°C to 38.13 ± 0.09°C). Different from the lack of effect observed in euthermic rats, when LPS was combined with PAG, febrile response to LPS was significantly blunted (rise of 0.58°C; P = 0.0317; n = 5-6 per group). Conclusion: The present findings suggest that peripheral H2S acts as a proinflammatory agent facilitating the development of endotoxic fever. Keywords: propargylglycine; lipopolysaccharide; gaseous neuromodulator; CSE; systemic inflammation. Financial support: FAPESP, CNPq, CAPES

PT.25 Intracerebroventricular administration of leptin increase physical activity but has no effect on metabolism in cold-acclimated rats. Tang GB, Wang DH Chinese Academy of Sciences –Zoology – Integrated Management of Pest Insects and Rodents

Chronic cold exposure stimulates thermogenesis in brown adipose tissue, resulting in fat mobilization and compensatory hyperphagia, and accompanied by a remarkable reduction in serum leptin levels. However, the behavioral and physiological roles of hypoleptinemia in cold adaptation are still not clear. We hypothesized that leptin is the keystone of the regulatory systems linking energy balance to cold adaptation. Intracerebroventricular injection of leptin has no effects on basal metabolism, adaptive thermogenesis and uncoupling protein 1. Serum ghrelin concentrations were decreased in response to leptin treatment. ICV infusion of leptin antagonist did not change the body temperature and ability of cold tolerance. We further treated animals with ICV infusion of leptin (5µg/day) with or without ghrelin (1.2µg/day) for cold-acclimated rats. Leptin administration resulted in increase of physical activity and decrease of hypothalamic melanin-concentrating hormone (MCH) gene expression. Central coadministration of ghrelin completely reversed the effects of leptin on physical activity, adiposity and hypothalamic MCH mRNA, but it could not block the anorectic effect of leptin. We present preliminary evidence that the regulation of leptin on energy expenditure is mainly mediated by physical activity but not by metabolism in cold-acclimated rats. Hypoleptinemia partially contributes to cold-induced hyperphagia, which might involve the elevation of MCH mRNA. Ghrelin was involved in the regulation of the effects of leptin on food intake, body fat, physical activity and hypothalamic MCH gene expression.

PT.26 Contribution of the dopamine receptor 1 (D1R) within the paraventricular nucleus in the heat stress-induced hyperthermia and hyperphagia. Guimarães JB1, Leite LHR2, Zheng, H3, Coimbra CC1, Patel KP4, UFMG – Fisiologia e Biofísica, 2UFJF – Fisiologia, 3University of Nebraska Medical Center – Cellular and Integrative Physiology, 4University of Nebraska Medical Center – Physiology

PT.28 Daily wheel running in mild heat improves heat tolerance and acclimation in mice: its relation to hypothalamic mechanisms. Tokizawa K Waseda University – Sport Sciences

Repeated exposure to moderate heat improves heat tolerance and acclimation. Exercise induces the improvement more effectively than just being at rest. The underlying central mechanisms of those phenomena have remained unclear. We tested, in mice, whether daily exercise in moderate heat augments heat tolerance and acclimation, and which is related to the neurogenesis and neuronal response in the hypothalamus.

Male mice were individually housed at 32°C (HE) or 25°C (NE). The mice in two groups had two-different exercise conditions: with (EXE) and without (CON) access to running wheels. After eight weeks, intra-abdominal temperature (Tb), MAP, heart rate (HR), core (Tcore) and tail (Ttail) temperatures were recorded in anesthetized rats after bilateral microinjection of CSF or SCH 39166, D1R antagonist (1 pmol/100 nL) into PVN during heat stress (n = 6 / group). Heat stress was induced by graded increase in the Tcore during 30 minutes. This stimulus promoted similar increase in Tcore between groups (ΔTcore: 2.6 ± 0.2°C, CSF vs. 2.4 ± 0.2°C, D1R antagonist; p > 0.05). However, blockade of D1R PVN attenuated the increase in Ttail induced by heat stress (ΔTtail: 3.6 ± 0.6°C, CSF vs. 2.1 ± 0.5°C, D1R antagonist; p < 0.05). Dopaminergic blockade into PVN attenuated RSNA (∆ΔRSNA: 135.2 ± 19.2 %, CSF vs. 61.8 ± 9.6 %, D1R antagonist; p < 0.05), as well as showed a tendency to attenuate MAP (∆ΔMAP: 21.3 ± 2.9 mmHg, CSF vs. 8.8 ± 4.1 mmHg, D1R antagonist; p = 0.07). Change in HR induced by heat stress was unaffected by D1R PVN blockade (∆ΔHR: 103.2 ± 13.3 bpm, CSF vs. 102.8 ± 12.4 bpm, D1R antagonist; p > 0.05). In summary, D1R PVN participates in increasing RSNA to heating, contributing to cardiovascular adjustments that influence core blood redistribution to the periphery. Furthermore, heating increases heat loss through peripheral vasodilation via D1R into PVN.
proliferation, was not observed in the hypothalamus in NE-CON mice. However, the immunoreactive cells were found in medial preoptic nucleus and dorsomedial hypothalamus in NE-EXE, HE-CON, and HE-EXE mice. These results may indicate that daily exercise and long-term exposure to mild heat, separately, are sufficient to improve heat tolerance and acclimation respectively, and their combined effect induces both improvements. Although neurogenesis in the hypothalamus may be responsible for these physiological adaptations, further possible reason will be presented based on another histological study.

PT 29
Activation of hemostatic pathways by exercise induced hyperthermia. Eijsvogels TM, Veltmeijer, MT, van Geffen, M, Thijssen, DH, van Heerde, WL, Hopman, MT. Radboud University Nijmegen Medical Centre – Physiology, Radboud University Nijmegen Medical Centre – Haematology

**Background:** Exertional heat stroke is a form of hyperthermia associated with a systemic inflammatory response potentially leading to multi-organ dysfunction. Retrospective studies indicated that patients with heat stroke have a sustained activation of coagulation, fibrinolysis and platelets. However, little is known about changes in haemostatic parameters in athletes without physical complaints. Therefore, the aim of this study was to determine changes in thrombin and plasmin generation after exercise induced hyperthermia 15 km run.

**Methods:** Core body temperature (telemetry system) was assessed before and at the finish line of a 15 km run in 16 participants (51±8 years, 31% female). Venous blood samples were collected pre- and immediately post-race. The Novel Haemostasis Assay was used to measure thrombin and plasmin generation simultaneously. This allows insight in the interaction between coagulation and fibrinolysis.

**Results:** All subjects completed the race, with an average speed of 11.2±1.2 km/h. Core body temperature increased from 37.7±0.5°C at baseline to 39.4±0.9°C at the finish. The time to thrombin peak decreased from 9.2±2.3 min to 8.1±1.0 min (p<0.05), while the thrombin peakheight significantly increased from 178±63 nM to 190±67 nM (p<0.001). In contrast, the plasmin peak-time increased from 28.4±9.5 min to 32.±10.9 min (p<0.05), with a decrease in plasmin peakheight from 4.3±4.0 nM to 2.7±2.1 nM (p=0.07).

**Conclusion:** An increase of 1.7°C in core body temperature stimulated coagulation by enhancing thrombin generation and reducing plasmin generation. These innovative **Results** suggest that exercise induced hyperthermia leads to activation of the coagulation pathway. Nevertheless, the clinical relevance of these findings has yet to be determined.

PT 30
Effect of hypoxic training on exercise thermoregulatory responses. Kounalakis SN, Eiken O, Mekjavic IB. Evelpidon Hellenic Military University – Human Performance-Rehabilitation Laboratory – Physical and Cultural Education, Royal Institute of Technology – Environmental Physiology, Jozef Stefan Institute – Automation, Biocybernetics and Robotics

**Background:** The potentiated exercise sweating response observed during acute hypoxia is diminished after a sleep high-train low (SH-TL) regimen. **Aim:** We tested the hypothesis that this decrease in evaporative heat loss reported after SH-TL is compensated by an increase in conductive/convective heat loss.

**Methods:** Nine male subjects participated in a 28-day SH-TL regimen. Before (pre-) and immediately after (post-) the SH-TL protocol, they performed a normoxic and hypoxic VO_{2peak} test, and three 30-min steady state trials on a cycle ergometer. In one trial the subjects inspired room air while exercising at 50% of normoxic VO_{2peak} (CT). In the remaining two trials, subjects exercised in hypoxia (FIO2: 12.5%), either at the same absolute (HAT) or relative (50% of hypoxic VO_{2peak}) workrate (HRT) as in CT.

**Results:** Despite similar exercise core temperature responses between pre- and post-SH-TL trials, sweating rate was potentiated in HAT pre-SH-TL [CT: 1.97 (0.04), HRT: 1.86 (0.03), HAT: 2.55 (0.05) mg·cm^{-2}·min^{-1}, p<0.05]. Post-SH-TL exercise-sweating rate was increased for CT, tended to be higher for HRT, and remained unchanged in HAT [CT: 2.42 (0.07), HRT: 2.01 (0.03), HAT: 2.59 (0.03) mg·cm^{-2}·min^{-1}]. This was accompanied by a higher mean skin temperature, higher muscle blood volume and lower forearm-fingertip difference.

**Conclusion:** The decrease in exercise evaporative heat loss following a 28-day SH-TL regimen was counteracted by an increase in conductive/convective heat loss. This is most likely a consequence of the hypoxic acclimatization. The potentiation of the sweating rate during normoxic exercise is attributable to the exercise training.

**Keywords:** Near infrared spectroscopy, sweating, hypoxic training, and altitude acclimatization, relative and absolute workrate
Results: Our data provide evidence that HI is not a physiological incompetence event. The transcriptome profile suggests that HI is accompanied by constitutive activation of gene markers even prior to exercising in the heat and different activation profile during HTT. Our analyses emphasize that there is a significant difference in the up-regulated clusters between the HI and the T phenotypes, and that the HI phenotype shows significant up-regulation of genes associated with (i) immune response (ii) signal transduction, and (iii) protein phosphorylation. Neither the immune, nor the protein amino acid phosphorylation clusters were visible in the T group. Constitutive changes in the HI vs. the T phenotype, measured prior HTT provided evidence of down-regulation of genes associated with DNA repair, transcriptional regulation, anti-apoptosis, coagulation and immune system. Conclusions: Exertional heat stroke induces both coagulopathy and immune dysfunction. Hence genes associated with these functions are possible good markers for the identification of HI individuals.

PT.32
Chronic absence of tail artery innervation impairs cutaneous heat loss during physical exercise in thermoneutral and warm environments. Lima MRM1, Pires W1, Fonseca, I.A.T.1, Wanner SP1, Coimbra CC2, Lima NRV1 1UFMG – Educação Física, 2UFMG – Fisiologia e Biofísica

This study investigated the chronic effects of the tail artery denervation on the thermoregulatory adjustments induced by exercise performed in thermoneutral and warm environments. For this purpose, 16 adult male Wistar rats were divided into two groups: animals submitted to the denervation of the ventral tail artery (DVTA) or to sham surgery (Sham-DVTA) as a control procedure. A temperature sensor was implanted into the peritoneal cavity. Rats were submitted to the exercise trials on a treadmill at 18 m/min until fatigued in both cool (25°C) and hot (35°C) conditions. Pulsatile arterial pressure was recorded by the aortic catheter and intraperitoneal temperature (Tb) by telemetry. Power spectral density was obtained using the fast Fourier transformation method. Spectral power components for very low- (VLF, <0.18 Hz), low- (LF, 0.18–1.0 Hz) and high-frequency bands (HF, 1.0–3.0 Hz) were obtained by means of power spectrum density integration.

During exercise in the heat, SHAM rats showed lower running performance (21.6 ± 2.6 min SHAM-Hot vs. 33.8 ± 5.7 min SHAM-Cool; p<0.05) compared with cool condition and SAD induced a more pronounced reduction in time to fatigue (13.5 ± 1.6 min SAD-Hot vs. 21.6 ± 2.6 min SHAM-Hot; p<0.05). The effects evoked by the chronic absence of arterial baroreflex suggest that the mechanism plays an important role modulating autonomic nervous system and exercise performance in the heat.

PT.34
Exercise intensity affects the rate of increase of frontal cortex temperature, but does not change the absolute value at the voluntary interruption of the effort. Kunstetter AC1, Wilke CF1, Madeira LG1, Lima MRM2, Wanner SP3, Rodrigues LOC3, Lima NRV4 1UFMG – Fisiologia do Exercício, 2UFMG – Fisiologia e Biofísica

Background: The aim of this study was to evaluate the cortical brain temperature at three different exercise intensities performed until the voluntary interruption of the effort.

Methods: Male adult Wistar rats (n=8) were implanted with a cerebral guide cannula in the right frontal cortex. After a recovery period, rats were familiarized to exercise on a treadmill for 5 days. Immediately before each trial, the thermistor for temperature measurement was inserted into the brain through the cannula. Animals were submitted to running exercise until
voluntary interruption of the effort at three different intensities: 18 m/min (V18), 21 m/min (V21), and 24 m/min (V24) (5% inclination). Cortical temperature was measured throughout the exercise. The rate of rise in cortical temperature was calculated by dividing the change in temperature by the total exercise time (TET). Ambient temperature was maintained at 25.1 ± 0.9°C.

**Results**: As expected, TET decreased with the increase in the exercise intensity (V24: 61.3 ± 12.5; V21: 150.7 ± 15.6; V18: 206.3 ± 17.4 min; p <0.001). Exercise induced marked increases in cortical temperature, and no differences among the three intensities were observed in the exercise at the moment of voluntary interruption of the effort (~40.1 – 40.4°C). Therefore, the rate of rise in cortical temperature was the greatest during exercise performed at 24 m/min.

**Conclusions**: At a fixed ambient temperature, exercise intensity influences both the rate of rise in cortical temperature and total exercise time, without affecting the absolute value of cortical temperature at which the effort was voluntary interrupted.

**PT.35**


**Background**: To determine an ambient temperature at which the ventromedial hypothalamic nucleus (VMH) temperature is not altered during physical exercise performed until the voluntary interruption of the effort (VIE).

**Methods**: Adult male Wistar rats received an implant of a unilateral guide cannula so that the tip of the cannula was aimed at the right VMH. After recovery from this surgery, the animals were subjected to a running exercise at 20 m/min until the VIE at two ambient temperatures: 12°C and 25°C.

**Results**: According to our preliminary Results, at a room temperature of 25°C, VMH temperature increased during exercise until the VIE (37.66 ± 0.04°C zero min vs. 39.26 ± 0.09°C VIE; n = 4; p = 0.001). However, at an ambient temperature of 12°C, VMH temperature was not changed during exercise until the VIE (37.19 ± 0.50°C zero min vs. 37.91 ± 0.34°C VIE; n = 3; p = 0.27). No differences were observed in the exercise time to the VIE between trials (68.75 ± 19.31 min at 12°C vs. 39.75 ± 7.44 min at 25°C; n = 4; p = 0.28).

**Conclusions**: A ventromedial hypothalamic nucleus thermal clamp was achieved during physical exercise performed at 20 m/min until the voluntary interruption of the effort at an ambient temperature of 12°C. Moreover, the hypothalamic thermal clamp did not change the exercise performance. However, it is possible that the lack of differences between experimental trials (i.e., with or without thermal clamp) in physical performance was due to the small sample size.

**PT.36**


**Aim**: To investigate performance during a self-paced exercise in warm ambient. **Methods**: At least 3 days before the exercise bout, nine individuals (26.89 ± 1.32 y) performed a progressive test to evaluate the maximal power output. In addition, the subjects underwent a familiarization trial prior to beginning of the experiments. During the experiments, the individuals performed 20 min of self-paced exercise cycling in a temperate (T) (23°C / 62% r.h.) or in a warm (W) (34°C / 65% r.h.) ambient. These trials were performed in a randomized and balanced fashion, separated by 7 days. During the exercise, the measurements of performance, rectal temperature (T_r) and heart rate (HR) were obtained at 1-min intervals, skin temperatures (T_s) were obtained every 2-min and ratings of perceived exertion (RPE) at 4-min intervals. Temperatures and HR data were analyzed using two-way ANOVA with repeated measures. When a significant effect was detected, post-hoc comparisons were made using Tukey’s. Averages were analyzed using the Student’s t-test. RPE was analyzed using the Friedman and Wilcoxon tests. For all analyses significance was set at p<0.05. Data are presented as means ± SE, except RPE, presented as median.

**Results**: The ambient did not influence the performance (T: 9.1 ± 0.3 km; W: 9.3 ± 0.3 km) or the final RPE (T: 18; W: 18). At the end of self-paced protocol, the T_w was higher in the warm trial (T: pre: 36.6 ± 0.06°C; post: 37.5 ± 0.06°C; W: pre: 36.8 ± 0.06°C; post: 37.7 ± 0.08°C), but the heat storage was similar in both conditions (T: 98.7 ± 11.2 J.m^{-2}.s^{-1}; W: 103.6 ± 9.8 J.m^{-2}.s^{-1}). The following thermoregulation adjustments to heat dissipation, in the warm ambient, were observed: increased sweat rate (T: 2.7 ± 0.5 g.m^{-2}.min^{-1}; W: 4.8 ± 0.7 g.m^{-2}.min^{-1}) skin temperature (T: 31.7 ± 0.3°C ; W: 35.1 ± 0.4°C) and in heart rate (T: 167 ± 3 bpm; W: 172 ± 3 bpm). **Conclusions**: The main finding of this study was that heat stress did not cause a decrease in performance in untrained subjects during a self-paced exercise. Moreover, in spite of the heat challenge, this mode of exercise allowed the subjects to choose an exercise workload which defended them against heat related problems. This reinforces the protective approach of fatigue.

**Keywords**: Fatigue; self-paced; thermoregulation; exercise.

**Financial Support**: FAPEMIG and CAPES

**PT.37**

Neuronal basis for the hypothermic effect of antiepileptic drugs with GABAergic mechanisms of action. Yakimova KS Medical University of Sofia – Pharmacology & Toxicology

In mammals since more than 30 years the gamma-aminobutyric acid (GABA) is known as the main inhibitory neurotransmitter within the brain. Many drugs used in treatment of epilepsy as benzodiazepine derivatives, valproates, barbiturates, as well as GABA-transaminase inhibitors exert its activity via GABAergic mechanisms of action. It has been shown also that many of these drugs cause hypothermia. Neurons in...
the preoptic area of the mammalian anterior hypothalamus (PO/AH), which respond to local temperature changes, are supposed to build a neuronal network, which takes part in the central control of body temperature. The aim of this study is to find a relationships between the changes in body temperature of rats from antiepileptic drug with GABAergic mechanisms of action and changes in temperature sensitivity of rat warm-sensitive hypothalamic neurons. Extracellular recordings were made from neurons in slices of the preoptic area/anterior hypothalamus (PO/AH) of rats, to investigate the effects of antiepileptic drugs from different pharmacological groups: phenobarbital, diazepam, sodium valproate and vigabatrin on temperature sensitivity of warm-sensitive PO/AH neurons. The investigated drugs phenobarbital, diazepam, sodium valproate and vigabatrin significantly increased temperature sensitivity (temperature coefficient, TC) in a warm-sensitive rat PO/AH neurons. Our Results are step of understanding the complicated mechanisms of action of the drugs on the level of central temperature controller – the neurons in the PO/AH. Our Results support the hypothesis that the substances which decrease body temperature, increase temperature sensitivity in warm-sensitive rat PO/AH neurons. Keywords: brain slices, extracellular recordings, GABA-acting drugs, temperature sensitivity, rats.

PT.38
Coping with systemic inflammation and sepsis: value of the fever-hypothermia switch. Steiner AA1, Liu E1, Lewis K1, Al-Saffar H1, Krall CM1, Corrigan JJ1, Singh A2, Musteata ML1, Bakshi CS3, Romanovsky AA4, Sellati TJ4 1Albany College of Pharmacy and Health Sciences – Pharmaceutical Sciences, 2Albany Medical College – Immunology and Microbial Disease, 3New York Medical College – Microbiology and Immunology, 4St Josephs Hospital and Medical Center – Systemic Inflammation Laboratory

Background: A switch from fever to hypothermia often occurs in severe cases of the systemic inflammatory response syndrome (SIRS) and sepsis. We evaluated how this switch in thermal state impacts the pathophysiology of SIRS/sepsis.

Methods: SIRS was induced by lipopolysaccharide (LPS, 5-18 mg/kg; aseptic model) or E. coli (0.5-1.0 x 10^10 CFU/kg; sepsis model) in conscious rats exposed to a cool (22.0-25.5ºC) or warm (28.0-31.5ºC) environment. Results: Rats in a cool environment developed hypothermia in response to LPS or E. coli, whereas rats in a warm environment did not (they only developed fever). Endotoxemia was unaffected by thermal state in the LPS model of SIRS. However, in the E. coli model, endotoxemia was suppressed in hypothermic rats compared to febrile rats. Neutrophil infiltration in lung tissue was similarly suppressed by hypothermia in the E. coli model, but not in the LPS model. Although these effects are expected to be beneficial, they may come at a cost since hypothermia resulted in accumulation of E. coli in the liver. Furthermore, hypothermic rats presented exaggerated hypotensive responses to LPS or E. coli, though this exaggeration did not result from an enhanced pro-inflammatory response and could represent a compensated physiological adjustment. Regardless of its possible costs, hypothermia alleviated abdominal organ injury (liver, kidneys and pancreas) in both the LPS and E. coli models. Hypothermia also reduced LPS-induced mortality and tended to reduce E. coli-induced mortality. Conclusion: A natural switch from fever to hypothermia may be an adaptive strategy in severe SIRS/sepsis. Keywords: sepsis, inflammation, shock, fever, hypothermia Support: American Heart Association; NIH; Albany College of Pharmacy

PT.39
Permanent changes in thermoregulation and cardiovascular response to cold stress in offspring of rats exposed developmentally to endocrine disruptors. Gordon CJ1, Johnstone A1, Grace C1, Aydin C2, Rogers JM1, Gilbert ME1 – 1US EPA – Toxicity Assessment, 2University of Uludag – Physiology

Developmental exposure to endocrine disrupting toxicants alters thermoregulation and other physiological processes of mature offspring. Maternal stress-induced elevations in corticosteroids (CORT) and/or changes in thyroid status are thought to be important mechanisms eliciting the thermoregulatory and cardiovascular dysfunctions in offspring. In one study, rats were exposed via drinking water from GD 6 through PND 21 to propylythiouracil (PTU), an antithyroid drug. Adult offspring were implanted with transmitters to monitor core temperature (Tc) and motor activity (MA). Male rats treated with 10 ppm PTU had a significantly reduced Tc but elevated MA an age of 6, 9, and 12 months. The hypothermic effects of PTU worsened with age. In another study, pregnant rats were treated orally on GD 15-20 to control vehicle, the CORT agonist dexamethasone (DEX) (0.1 mg/kg), or atrazine (ATZ) (125 mg/kg). ATZ, a widely used herbicide, increases CORT in female rats. Adult offspring were implanted with telemetry units to monitor Tc, blood pressure (BP), heart rate, and MA. Rats treated with DEX or ATZ had significantly elevated BP but normal Tc under resting conditions. Cold exposure (Ta=8ºC) revealed a significant hypertensive response to cold stress in the DEX and ATZ rats. These studies demonstrate that developmental insults that affect the thyroid or adrenal systems lead to permanent changes in thermoregulatory control and cardiovascular sensitivity to cold stress. This is an abstract of a proposed presentation and does not reflect US EPA policy.

PT.40
Interstitial calcium concentration modulates human eccrine sweating. Metzler-Wilson K1, Sammons D2, Wilson TE3 1Lebanon Valley College – Physical Therapy, 2HCOM-Ohio University – Specialty Medicine, 3HCOM-Ohio University – Biomedical Sciences

Calcium is an important second messenger in eccrine sweating, with both internal and external sources being 37
identified. Modulation of calcium concentration in the external medium of isolated rhesus monkey palm sweat glands modulates eccrine sweat gland function (Sato & Sato, *Am J Physiol*, C113-20; 1981). It is unclear if *in vivo* modulation of interstitial calcium levels has the capacity to modulate sweat rate in human skin. We hypothesized that lowering interstitial calcium levels would cause a rightward shift in the sweat rate (SR) to acetylcholine (ACh) dose-response relation. 9 healthy subjects received 7 ACh doses (1x10^-7 to 1x10^-1 M, 10-fold increments) with and without calcium chelator (12.5 mg/ml EDTA) via forearm intradermal microdialysis. Capacitance hygrometry measures of SR (expressed as change from baseline) were completed directly over the microdialysis membrane. SR to ACh dose-response modeling via nonlinear regression curve fitting (mean R^2 0.97±0.05 with and 0.95±0.03 without EDTA) identified the maximal responsiveness (Emax) and ED_{50} (dose of ACh causing 50% of Emax). EDTA right shifted the ED_{50} (0.136±0.078 M) compared to ACh alone (0.044±0.032 M; p<0.05). Emax was not different between groups (0.60±0.078 and 0.58±0.34 mg/cm^2/min, respectively; p>0.05). The protocol was repeated in 5 subjects, measuring skin blood flow via laser-Doppler flowmetry. Neither Emax nor ED_{50} was significantly different between groups. Thus, local in vivo calcium chelation has the capacity to attenuate the cholinergic sensitivity of eccrine sweat glands. These data suggest that interstitial calcium plays a functional role in eccrine sweating in human skin. 

**Keywords**: Sweat glands, calcium, microdialysis, cholinergic agonists, skin blood flow

**PT.42**

Pretreatment with glutamine blocks the increase in intestinal permeability and bacterial translocation induced by passive hyperthermia. Wanner SP^1, Soares ADN^2, Costa KA^2, Santos RGC^2, Fernandes SOA^3, Coimbra CC^1, Cardoso VN^2 1UFMG – Fisiologia e Biofisica, 2UFMG – Alimentos, 3ICB-UFMG – Fisiologia e Biofisica, 4UFMG – Análises Clínicas e Toxicológicas

**Background**: The aim of this study was to evaluate the effect of pretreatment with L-glutamine on the intestinal permeability (IP) and bacterial translocation (BT) in mice subjected to passive hyperthermia. Methods: After weaning, male Swiss mice underwent a surgical implantation of a temperature sensor into the peritoneal cavity for recording body core temperature (T_core). After 5 days of recovery, the mice were divided in three groups and treated with isocaloric and isonitrogenous diets for 7 days: standard AIN-93G diet (C); standard AIN-93G diet and hyperthermia (H); AIN-93G diet supplemented with glutamine (500 mg/kg/day) and hyperthermia (H-Glut). On the eighth day, animals received DTPA radiolabeled with technetium (99mTc-DTPA) by gavage for analysis of IP. The H and H-Glut groups were placed in a climate chamber at 39°C for 2 h to induced hyperthermia, whereas the C group remained at room temperature (24°C). BT was assessed using 99mTc-Escherichia coli administered by gavage. Results: Passive heating increased T_core (~41°C), which led to an increase in IP (10-fold higher compared with C; 3 h after exposure to heat) and in BT to the blood, liver and lungs. Although the pretreatment with glutamine did not alter the increase in T_core, it prevented the higher IP and BT to the blood and liver caused by hyperthermia. Conclusions: Pretreatment with glutamine preserves the intestinal barrier integrity and reduces the bacterial translocation to the blood and liver during passive hyperthermia. Dietary glutamine may represent an important intervention to decrease the incidence of heat stroke.

**PT.43**

Interleukin (IL)-6 and Endothelin-1 (ET-1) may not be involved on Poli I:C fever. Bastos-Pereira AL, Fraga D, Zampronio AR UFPR – Farmacologia

This work compared the involvement of IL-1β, IL-6, TNF-α and ET-1, on febrile response induced by TLR3 agonist Poli I:C and TLR4 agonist E. coli LPS. Male Wistar rats (180-220g) were implanted with dataloggers i.p. for temperature measurement and with an i.c.v. cannula for drug administration. Experiments
were conducted at 28±1°C, body temperature was measured 2h before any injection up to 6h. Poli I:C (3-300µg.kg⁻¹, i.p) induced a dose-dependent febrile response up to 1.2°C that started at 2h, peaked at 3h and returned to normal around 4h. TNF-α, IL-1β and IL-6 were measured on CSF and plasma 1, 2 or 3h after LPS (50µg.kg⁻¹, i.p) and Poli I:C (300µg.kg⁻¹, i.p), respectively, by ELISA. An increase of plasmatic TNF-α and IL-1β was observed on LPS-stimulated animals (238.3±79 and 928.4±122.9 pg.ml⁻¹) compared to saline group (below detection for TNF-α and 5.56±5 pg IL-1β.ml⁻¹). Poli I:C induced a less expressive increase: a sample with 241.53pg.ml⁻¹ and others below detection for TNF-α and 207.3±43.4pg.ml⁻¹ for IL-1β. Both CSF and plasma IL-6 levels were increased on LPS-treated group (227.2±69.4 CF and 585.4±374.8pg.ml⁻¹ plasma), while no significant increase was seen on Poli I:C-treated group (76.13±11.25 CSF and 101.2±25.9pg.ml⁻¹ plasma), compared to saline group (66.50±2.5 CSF and 62.79±8.7 pg.ml⁻¹ plasma). Treatment of the animals with the ETB antagonist BQ788 (3pmol, i.c.v.) reduced the febrile response induced by LPS but not that induced by Poli I:C. These Results suggest that Poli I:C-mediated febrile response is not dependent on IL-6 and ET-1 release. Keywords: poli I:C, endothelin, BQ788, interleukin-6

PT.44
Previous freezing cold injury does not affect temperature-induced digit vascular responses. Mekjavic, IB1, Gorjanc J2, McDonnell AC3, Milečnik, M4, Eiken, O5, Morrison SA6 1Jozef Stefan Institute – Automation, Biocybernetics and Robotics, 2Hospital of the Brothers of St. John of God, 3Jozef Stefan International Postgraduate School, 4University Medical Centre – Nuclear Medicine, 5Royal Institute of Technology – Environmental Physiology, School of Technology and Health, 6Jozef Stefan Institute – Automation, Biocybernetics and Robotics

Methods: Ten elite alpinists (8 males and 2 females), who suffered at least one instance of cold injury and CORR digits.

Results: No significant differences were observed in Td between INJ (N=6) and CORR fingers. NISS toes (N=26) were significantly warmer than NICO toes (34.0±1.8 v 32.5±2.4°C, P=0.034) during warming. INJ toes were colder throughout the cold bath compared to CORR toes (10.0±1.4 v 11.2±2.3°C, P=0.005). There were no differences in Td during recovery between INJ and CORR digits.

Conclusion: Vasodistraction and vasodilatation, as reflected in Td, are not compromised by previous freezing cold injury.

Keywords: freezing cold injury, amputation, alpinist, blood flow, hypothermia

PT.45
Effects of the PPAR-γ agonist Rosiglitazone on LPS-induced systemic inflammation and on mitochondrial biogenesis in old and young rats. Koenig S1, Wenz T2, Gerstberger R3, Roth J4, Rummel C1, Justus-Liebig-University Giessen, Germany –Veterinary Physiology and Biochemistry, 2University of Cologne – Genetics

Background/Aims: Aging induces a low grade inflammatory response and to stimuli of the innate immune system such as lipopolysaccharide (LPS) are altered. One main underlying factor of these changes might be a functional mitochondrial decline with aging. Rosiglitazone (RZG) is a peroxisome proliferator-activated receptor (PPAR) agonist with anti-inflammatory properties and induces a key regulator of mitochondrial biogenesis, PPARγ co-activator-1alpha (PGC-1α). Here, we aimed to further investigate changes occurring with age in the sickness response and in the signaling pathways during systemic LPS-induced inflammation and to test potential beneficial effects of Rosiglitazone.

Methods: Old (24 months) and young (2 months) rats were pretreated with Rosiglitazone or solvent followed by an injection of LPS (100 µg/kg) or saline. 24 hours after stimulation brain, blood and liver were withdrawn for further analyses.

Results: Old rats showed prolonged fever and aggravated sickness symptoms after LPS stimulation compared to young rats. However, pretreatment with RZG had no significant effect on fever or other sickness responses. The basal mRNA levels of markers of mitochondrial biogenesis like PGC-1α and IL-6 were higher in old than in young rats and were further increased by RZG in the liver, but not in the hypothalamus. LPS-injection reduced the levels of mitochondrial markers in the liver, thereby abolishing the effect of RZG.

Conclusion: These Results suggest a compensatory upregulation of mitochondrial markers with aging and a down-regulating role of LPS on these markers. A beneficial effect of Rosiglitazone on the fever response was not detectable.

Keywords: Rosiglitazone, aging, PGC-1α, sickness behavior, lipopolysaccharide

PT.46
CCL3/MIP1α induces calcium signaling in cells from rat pre-optic area microcultures but not TNF-α or IL-6 synthesis. Soares DM1, Ott D2, Souza GEP3, Roth J2

46 45
Hypothermia following exertional heatstroke treatment-three case reports. Moran DS1, Makrantz C2, Shapiro H.

Keywords: Chemokines, fever, Calcium mobilization, Pre-optic area.

PT.47 Hypothermia following exertional heatstroke treatment-three case reports. Moran DS1, Makrantz C2, Shapiro Y1, Heled Y2. Ariel University Center of Samaria, 2Heller Institute – Sheba Medical Center

Background: During the last two years we experienced three cases of hypothermia following treatment of suspected exertional heatstroke events in the Israeli Defense Forces (IDF). These cases are presented together with our recommendations for treatment in similar situations. Cases: Two young soldiers (19-20 yrs) participated in marches (12 and 21 km) and another soldier (22 yrs) participated in a physical sorting process. All three soldiers collapsed during the activity and were diagnosed as suffering from exertional heat stroke. Notably, these three cases occurred during the winter. Core (rectal) temperature at the time of collapse was measured in only one soldier (40.0°C). Treatment: According to IDF regulations, the three patients were cooled by splashing them with a copious amount of tap water. Core temperature was measured after 30-45 min and was 33.0°C in one case and 34.5°C in the other two cases. The three soldiers were fully recovered within three days. Discussion: Exertional heat stroke requires an immediate cooling treatment in order to avoid deterioration that can result in fatal multi-organ failure. However, overcooling can cause hypothermia (below 35.0°C), with all the associated risks. Conclusions: In order to avoid hypothermia while cooling a hyperthermic subject it is critical to monitor core temperature by repeated or continuous rectal temperature measurements. We recommend that cooling should be stopped, particularly during cold climate conditions, at 38.0°C body core temperature.

PT.48 Modification of central sudomotor mechanism and sweat gland function induced by long-term tennis training in relative active heat loading. Kim TW1, Shin YO1, Lee JB2, Min YK2, Yang HM2. Soonchunhyang University - Health Care, 2Soonchunhyang University – Physiology

The study sought to determine the modification of central sudomotor mechanisms and sweat gland function by long-term tennis training (LTT). Fifteen sedentary (control) and 20 tennis-trained (trainee) subjects (VO2max, 43.2±5.1 vs. 59.4±3.7 ml·kg⁻¹·min⁻¹; body mass index, 23.5±3.7 vs. 17.3±2.5; body fat, 22.5±4.8 vs. 16.3±2.9%; < 0.001) sat in a chairperson in a relaxed posture for 60 min and then performed 30 min running tests at 60% VO2max (active heat loading, AHL) in a thermoneutral climate chamber (temperature, 25±0.5°C; 60±3 % relative humidity). The tympanic temperature (Tty), local skin temperatures (chest, upper arm, thigh, and leg) and sweating rate, activated sweat gland density were measured during AHL. The Tty threshold for sweating was lower in trainee than control (p< 0.05) and sweat onset time on local parts (chest, abdomen, back and thigh) was shortened in trainee (p< 0.001). The local sweat volume, activated sweat gland on torso (chest, abdomen, upper back, lower back) and limb (upper arm, forearm, thigh, leg), activated single sweat gland output and whole body sweat loss volume were significantly higher in trainee than control subjects. In Conclusion, the Tty threshold for sweating was lower in trainee by changing the central sudomotor drive and increases-regulated responsiveness of sweat gland function.

PT.49 Regulation of body temperature by free-living vervet monkeys (Chlorocebusaethiops). Fuller A1, Rabe K1, Mistry A1, Barrett L2, Henzi P2, Meyer L1, Mitchell D1, Helem R2. 1University of the Witwatersrand – Physiology, 2University of Lethbridge – Psychology

Background: Even without the predicted consequences of climate change, about one-third of primate species are faced with extinction. We hypothesize that individual vervet monkeys, as long-lived, slow-reproducing animals with complex social structures,
increasingly will be faced with challenges requiring them to trade-off social status, and likely reproductive success, for their own physiological wellbeing. 

**Methods:** In the first part of our long-term study on the phenotypic plasticity of free-living vervet monkeys, we used intra-abdominal miniature data loggers to measure body temperature every 5-min in nine animals (6 female, 3 male). We captured monkeys from troops of habituated animals, surgically implanted data loggers and released monkeys back into the reserve. Monkeys were recaptured after 6-9 months and temperature loggers were removed during surgery. **Results:** The monkeys were subjected to globe temperatures that fluctuated between -4°C and 51°C. Daily body temperature (mean 38.14 ± 0.05 °C) varied, on average, between 37.19 °C and 39.03°C, with a peak at about 17:00 and a trough at 04:00. While body temperature rose faster on hot compared to cool days, monkeys defended their body temperatures effectively at high environmental heat loads. Minimum body temperature within a relatively narrow range, largely as a result of behavioural modifications. **Conclusion:** In the face of varying environmental factors, monkeys with access to water and food, and without concomitant stress associated with pregnancy or illness, maintained body temperature within a relatively narrow range, largely as a result of behavioural modifications. Keywords: Thermoregulation, Primate Behaviour, Microclimate

**PT.50**

Development of behavioral thermoregulation model for evaluation of outdoor thermal environment. Kurazumi Y¹, Tsuchikawa T², Fukagawa K³, Yamato Y⁴, Matsubara N⁵, Horikoshi T⁶ ¹Sugiyama Jogakuen University – Life Studies, ²University of Hyogo – Human Science & Environment, ³Hiroshima International University– Engineering, ⁴Kure National College of Technology – Architecture and Structural Engineering, ⁵Kyoto Prefectural University – Environmental Sciences, ⁶Nagoya Institute of Technology – Techno-Business Administration

In outdoor environment, the effect on the human body by means of physical environmental factors that compose the sensational and physiological temperature is remarkably large in comparison to indoor environment. Although the environmental factors can be specified, it is necessary to predict human reactions at evaluation of outdoor environment. However, previous thermoregulation model could not evaluate the outdoor environmental factors. The purpose of this paper is to propose and develop human thermoregulation model for behavioral thermoregulation in outdoor environment in order to make predictable mean skin temperature for evaluation of outdoor environment. This is based on Gagge’s Two-Node model and has three body parts that is divided into direct solar radiation; indirect solar radiation; heat conduction. Each body part consists of core and skin layers. This considers effects of short-wave solar radiation, long-wave thermal radiation and heat conduction. To verify this model which express the influence of outdoor thermal environment upon the human body, experiments were conducted. It was shown from the comparison between mean skin temperatures of the predicted from the behavioral thermoregulation model developed by authors and the obtained ones by experiments that the predicted mean skin temperature agreed well with those by the experiments. It was shown from the relation between outdoor environmental index ETFe and mean skin temperature that it is possible to make the effects due to outdoor environment factors, short-wave solar radiation; heat conduction etc., quantitatively explicit. It was made clear that this model is valid to predict mean skin temperature in outdoor environment.

**PT.51**

Partial removal of brown adipose tissue enhances humoral immunity in warm-acclimated Mongolian gerbils (Merionesunguiculatus). Yang D, Xu Y, Wang DH State Key Laboratory of Integrated Management of Pest Insects and Rodents –Zoology, Chinese Academy of Sciences

**Backgrounds and Aims:** Rodent species living in temperate region experience marked seasonal fluctuations in temperatures. High thermoregulatory demands during winter usually weaken immune function. Brown adipose tissue (BAT) plays a crucial role in adaptive thermoregulatory process. We hypothesized that BAT participates in the regulation of seasonal immune function. The aim of the present study is to examine the trade-off between thermoregulation and immune function and the potential role of BAT in regulating seasonal changes in immune function in Mongolian gerbils. **Methods:** We surgically removed the interscapular BAT (34% of total BAT) in male gerbils, and subsequently acclimated them to either warm (23 ± 1°C) and cold (4 ± 1°C) conditions. Gerbils were then challenged with innocuous antigens and the immune responses were measured. **Results:** Resting metabolic rate (RMR) and nonshivering thermogenesis were increased under cold conditions. However, the cost of thermoregulation during cold acclimation did not suppress T-cell mediated immunity and humoral immunity or decrease spleen mass, thymus mass and white blood cells. Partial removal of BAT significantly enhanced humoral immunity in warm-acclimated, but not in cold-acclimated gerbils. T-cell mediated immunity, white blood cells and immune organs were not affected by BAT removal under both warm and cold conditions. **Conclusion:** Collectively, our results imply that BAT has a suppressive effect on humoral immunity in warm-acclimated gerbils and differential effects of BAT on humoral immunity under different temperatures might be benefit to their survival.

**PT.52**

Habitation of thermal sensation, but not in thermoregulation, following repeated daily exposure to menthol in humans. Gillis DJ, Weston N, House JR,
Selective brain cooling as a water conservation \( \text{menthol (M 0.05%; n=8), 0.2% l-menthol (M 0.2%; n=8). Each participant completed eight exposures over five days; on Monday (20°C, 50% RH) they were sprayed with 100mL of solution and undertook 40-minutes of cycling at 45% of their peak power (Ex1), from Tuesday to Thursday (30°C, 50% RH) they were sprayed twice daily with the same solution whilst resting, Friday was a repeat of Monday’s test (Ex2). TS, rectal and skin temperature, skin blood flow and sweat rate were compared by exercise condition and spray group (and interaction) using two-way repeated measures ANOVA (alpha=0.05).

Results: There was no significant difference (P>0.05) in heat storage by spray group or exercise condition. TS differed by exercise condition \((P=0.017)\) and spray group \((P=0.047)\), with an interaction \((P = 0.015)\). Specifically, \(M_{0.2}\) induced significantly cooler sensations than CON during Ex1 \((P<0.01)\), but not during Ex2 \((P>0.05)\), indicating an habituation of TS after repeated exposure to \(M_{0.2}\). This was not observed in \(M_{0.05}\) \((P>0.05)\).

Conclusion: The cooling influence of 0.2% menthol seems to habituate after repeated daily exposures (reject the null hypothesis), with no change in heat storage (accept the null hypothesis).

Keywords: Menthol, thermal sensation, thermoregulation, habituation, human

PT 54
Seasonal variation of core temperature and sweat rate in obese subjects. Sato M, Kanikowska D, Iwase S, Shimizu Y, Nishimura N, Inukai Y, Sugenoja J

Aichi Medical University – Physiology

Obesity has become a major health challenge worldwide. In Japan, 28.6% men and 20.6% women is more than BMI 25 kg/m\(^2\). We investigated the seasonal variations of core temperature and sweat rate in obese subjects in Japan. 5 non-obese (BMI, 23.2 ±2.9 kg/m\(^2\)) and 5 obese (BMI, 32.0±4.9 kg/m\(^2\)) men participated in this experiment at latitude, 35°10’ and longitude, 136°57.9’.

The average atmospheric temperature was 25–30°C in summer and 5–10°C in winter. Core temperature and sweat rate were measured during leg water immersion at 42°C for 30 min in 26°C, 50%RH.

The relationship between core temperature and sweat rate were significantly different between summer and winter in obese, which showed the lowered sweat rate to core temperature in winter. Our data showed that the thermoregulatory responses were lower in obese than in control, special in winter.
winter. Our study suggests that it needs to be taken
care of blood pressure control in winter in obese.

Keywords: obese, season, blood pressure

PT.56
Thermoregulation of free-living cheetah, Acinonyx jubatus. Hetem RS\textsuperscript{1}, de Witt B\textsuperscript{1}, Fick LG\textsuperscript{1}, Meyer, L\textsuperscript{1}, Maloney SK\textsuperscript{2}, Mitchell, D\textsuperscript{1}, Fuller A\textsuperscript{1}
\textsuperscript{1}University of the Witwatersrand – Physiology, \textsuperscript{2}University of Western Australia – Physiology

Background: Cheetahs are famed as the fastest land animals on earth and are one of the few cats that are predominantly diurnal, doing almost all of their hunting during daylight hours. The combination of extreme exertion and high heat loads may compromise thermoregulation, yet very little is known about the thermoregulation of free-living cheetah. Laboratory studies suggest that cheetahs deal with high heat production during high-speed sprints by allowing the body temperature to increase substantially to store the heat that is produced.

Methods: To test if such a strategy indeed exists in free-living cheetah, we implanted six cheetah (Acinonyx jubatus), from AfriCat’s Cheetah Rehabilitation Programme, with abdominal temperature and activity data loggers. Each animal also was equipped with a tracking collar. For seven months, the cheetah ranged freely within 4000 ha TUSK Cheetah Rehabilitation Camp, Okonjima, Namibia.

Results: Mean (38.3±0.2°C) and minimum (37.2±0.3°C) daily body temperatures did not change over the study period. Maximum daily body temperature (39.7±0.3°C) and the amplitude of body temperature rhythm (r²=0.07, P<0.0001) varied between 15 and 40°C over the study period.

Conclusion: In general, cheetah regulated their body temperature within narrow limits. During hunts, body temperatures increase, but body temperature it did not appear to limit the extent or duration of a hunt.

Keywords: Biologging, Body temperature, Activity, Hunting, Felidae

PT.57
Finger and toe temperature responses to cooling and warming in elite alpinists with and without previous freezing cold injury. Morrison SA\textsuperscript{1}, Gorjanc J\textsuperscript{2}, McDonnell AC\textsuperscript{3}, Milinski, M\textsuperscript{4}, Elken, O\textsuperscript{5}, Mekjavic, IB\textsuperscript{1}
\textsuperscript{1}Jozef Stefan Institute – Automation, Biocybernetics and Robotics, \textsuperscript{2}Hospital of the Brothers of St. John of God, \textsuperscript{3}Jozef Stefan International Postgraduate School, \textsuperscript{4}University Medical Centre, \textsuperscript{5}Royal Institute of Technology – Environmental Physiology, School of Technology and Health

Background: We have previously reported that alpinists with prior freezing cold injury (FCI) had poorer cold-induced vasodilatation than non-injured alpinists.

AIM: To compare digit rewarming rate following cold immersion in alpinists with and without prior FCI.

Methods: Alpinists with previous FCI requiring digit amputation (INJ: male N=8, female N=2), and non-injured alpinists (CON: male N=10) successively immersed their hands and feet in warm (35°C) and cold (8°C) water for 5 and 30 min, respectively. Infrared thermographs were taken of the hands and feet (dorsal-side) at baseline, immediately after the warm and cold water immersions, and at mins 5 and 10 of recovery. Digit temperatures were examined at the point of the nail bed, and in the case of amputation, on the dorsal surface proximal to injury.

Results: The INJ alpinists’ 2nd, 3rd and 4th fingers were colder immediately post cold bath, and at mins 5 and 10 of recovery, compared to the CON alpinists. The INJ alpinists had colder injured fingers at baseline (26.4±5.8 v 28.5±5.4°C) and after the 35°C bath (32.2±2.0 v 34.5±0.5°C) compared to their own, uninjured fingers on the unaffected hand (P=0.008). Their injured toes were warmer immediately post cold bath compared to their toes on the uninjured foot (9.2±1.5 v 8.7±1.4°C).

Conclusions: Despite the reported predominance of FCI in the feet, there were no differences in toe temperatures between alpinist groups.

Keywords: freezing cold injury, amputation, alpinist, Infrared thermography

PT.58
Low environmental temperature and obesity. Van Marken Lichtenbelt WD NUTRIM School for Nutrition, Toxicology and Metabolism of Maastricht University Medical Center – Human Biology

Obesity is nowadays a major global public health problem. Although food intake is one of the major causes, obesity is generally taken as a multifactorial problem. One of the causes may be the homoeothermic living conditions (within our thermoneutral zone) that characterize our western society.

The thermal environment affects energy expenditure as well as energy intake. Mild cold can increase energy expenditure substantially by means of nonshivering thermogenesis. Our Results from respiration chamber experiments show that in response to a mild cold environment obese subjects show blunted nonshivering thermogenesis. This was related to changes in skin temperature gradients. Obese subjects had significantly lower proximal skin temperatures than their lean counterparts. Obese make more use of tissue insulation to protect core temperature. These Results can be linked to the presence of brown adipose tissue (BAT) and to skeletal muscle mitochondrial uncoupling.

We showed that BAT activity was negatively related to the level of overweight (body mass index and body fat percentage). We also show that after weight reduction BAT activity can increase. The Results suggest that: 1) during the development of overweight the NST capacity
PT.59

Acclimation to heat – evident from a Poincaré Plot analysis of heart rate variability. Epstein Y, Heled Y, R Kobo, Levitan J, Ketko L, Moran DS

Medical Center – Heller Institute of Medical Research, \( ^2 \)Ariel University Center – Physics, \( ^3 \)Ariel University Center – Medical Sciences

**Aim:** Acclimation to heat is a time-dependent process. The present study was intended to investigate the efficiency of the autonomic nervous system (ANS) during heat acclimation.

**Methods:** Ten healthy young males were acclimated for 6 consecutive days to 40°C and 40% relative humidity (daily exposure: 120 min, exercising on a treadmill (5km/h, 4%), dressed in shorts). Rectal temperature (Tre) was measured by a rectal thermistor and RR intervals were logged (Polar RS800). Sweat rate was calculated from differences in weight and corrected for fluid intake. ANS efficiency was assessed by investigating the Poincaré Plot applying the Multiple heart rate variability (HRV) analysis. Specifically we looked at two parameters during the 2nd hour of each exposure: the dy/dx ratio, depicting the peak density on the y and x axes, and the quadripole parameter Qyy that describes the shape of the plot.

**Results:** At the end of the exercise session a reduction (from day 1 to day 6) in Tre from 38.1±0.3 to 37.6±0.2°C (p<0.01) and in HR from 122±2 to 117±2 bpm (p<0.01) were noted. Sweat rate increased from 550±70 ml/h to 610±20 ml/h (NS). The dy/dx ratio increased from 2.38±0.53 to 2.60±0.66 (p<0.01) and the Qyy parameters decreased from -610±258 to -560±956 (p<0.05).

**Conclusions:** The increase in the dy/dx ratio and the decrease in the Qyy parameter are markers of enhanced efficiency of the ANS. It can thus be concluded that following a six-day acclimation program the ASN becomes more efficient. This can serve as a surrogate marker for the effectiveness of the acclimation process.

**Keywords:** heat acclimation, exercise-heat stress, heart rate variability (HRV), autonomic nervous system (ANS), physiological strain

PT.60

Do older adults store more heat during work in the heat?: A calorimetric perspective. Kenny GP, Larose J University of Ottawa – Human Kinetics

**Background:** Older adults demonstrate a reduced local sweating and skin vasodilation response during passive heat stress. However, regional differences in the pattern of response have been reported. Similar age-related reductions in local sweat rate and skin perfusion have also been found for middle-aged and older individuals compared to younger adults during exercise in the heat. It remains unclear however if the age-related attenuation in local heat loss responses is paralleled by reductions in whole-body heat loss during work in the heat. **Purpose:** We investigated the effects of age progression on heat balance during intermittent exercise in the heat. Whole-body heat loss (\( \Delta H_l \)) and changes in body heat content (\( \Delta(\text{Tre}) \)) were measured using simultaneous direct and indirect calorimetry.

**Methods:** Five healthy young (28±4), middle-aged (45±3), and older adults (61±4) matched for fitness and body composition performed four successive bouts of 15-min cycling at a constant rate of heat production of ~400 W, each separated by 15-min rest at 35°C. **Results:** A lower rate of \( \Delta H_l \) was observed in older adults compared to the middle-aged and younger adults for all exercise cycles. No differences were observed during the recovery period. Responses were similar between middle-aged and younger adults. Ultimately, a greater cumulative \( \Delta(\text{Tre}) \) was observed for the older adults (268 kJ) as compared to the younger (180 kJ) and middle-aged (191 kJ) adults. **Conclusion:** Older adults demonstrated a decrease in whole-body heat loss during exercise in the heat relative to their middle-aged and younger counterparts.

PT.61

Effect of hypoxia and bedrest on peripheral vasoconstriction and sleep quality. McDonnell A C, DolencGroiselj L, Jaki Mekjavic, IB, Eiken, O, Mekjavic, IB, Jozef Stefan Institute – Automation, Biocybernetics and Robotics, \( ^2 \)University Clinical Centre Ljubljana – Clinical Neurophysiology, \( ^3 \)University Clinical Centre – Eye Clinic, \( ^4 \)Royal Institute of Technology – Environmental Physiology – Technology and Health, \( ^5 \)Jozef Stefan Institute – Automation, Biocybernetics and Robotics

**Background:** Lunar and planetary habitats will expose occupants to reduced gravity combined with hypoxia. **Aim:** To assess whether the previously observed \(^1\) inactivity-induced reduction in peripheral perfusion is augmented by hypoxia, and whether the decrease in perfusion causes sleep disruption \(^2\).

**Methods:** 11 males participated in two 10-d bedrest (BR) trials. In one, the ambient gas mixture was normoxic (N-BR), and in the other hypoxic (H-BR; simulated altitude 4000m). During BR days 1 and 10 we measured: forearm-fingertip skin temperature gradient (\( \Delta T_{\text{f-f}} \), index of peripheral perfusion), tympanic temperature, and full night polysomnography. Retinal scans obtained before and after the interventions assessed the presence of any altitude retinopathy (index of altitude sickness).

**Results:** There was no evidence of altitude retinopathy, although several subjects reported mild headaches during the first hours at altitude. There was a significant reduction in peripheral perfusion on day 1 of H-BR, which persisted until day 10. Peripheral perfusion was unchanged on day 1 of N-BR, and decreased on day 10, such that there was no difference between N-BR and H-BR. During night sleep percentage of light sleep...
(stage 1), and the latency of deep sleep (stage 3 and 4) were greater on day 1 than on day 10 in H-BR.

**Conclusions:** BR-induced progressive peripheral vasoconstriction is not augmented by hypoxia. The improvement in sleep quality despite the prevailing vasoconstriction in H-BR, is most likely due to hypoxic acclimatization.

**Acknowledgements:** Supported by the European Space Agency.


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