Laboratory of Molecular Neuroendocrinology

Department of Endocrine Neurobiology

Head of Laboratory:
Krisztina J. Kovács PhD

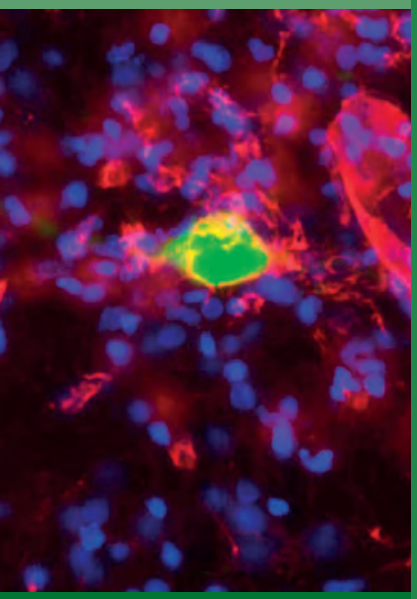
Mission statement

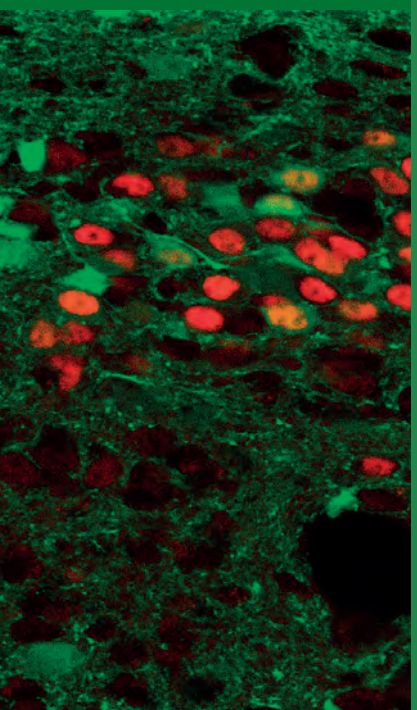
The brain orchestrates physiological responses to exogenous and endogenous stress challenges that serve adaptation. These responses are mediated by largely overlapping brain circuits of the limbic system, the hypothalamus and the brain stem. The final output is modulated according to the genetic background, current hormonal status and the overall physiological state of the organism, as well as on the epigenetic programming of early life events and previous stress experience.

The overall goal of our research is to reveal the pathways and mechanisms with which stress is perceived, processed and transduced into integrated neuroendocrine-, metabolic-, autonomic-, immune and behavioral responses. We aim to understand the assembly of neuronal circuits that are specifically recruited by physiological and psychological challenges, to identify signaling molecules that affect communication in these networks, and to study their regulation under stress. We are currently engaged in projects that aim to reveal interactions between immune-metabolic- and stress regulation. The research at the Laboratory of Molecular Neuroendocrinology involves combinations of various functional anatomical, molecular biological and physiological techniques from the molecular to the systems levels.

Understanding the neurobiology of stress by focusing on the brain circuits and genes that are associated with, or altered by, the stress response will provide important insights into the brain mechanisms by which stress affects psychological and physiological processes. Our current research focuses on the relationship between inflammation- stress- and neurological disease.

In addition to a strong research program, we are committed to translate this knowledge into the development of new treatment strategies for the prevention of stress-and inflammation-related disorders.





Senior Scientists: Ádám Dénes PhD, Szilamér Ferenczi PhD
PhD students: Rókus Kriszt, Ágnes Polyák and Zsuzsanna Winkler
Scientists Jr: Dániel Kuti and Bernadett Martinecz
Undergraduate students: Ágnes Gyöngy, Dóra Kővári and Edina Zelei

Functional Neuroanatomy of Stress-related Brain Circuits

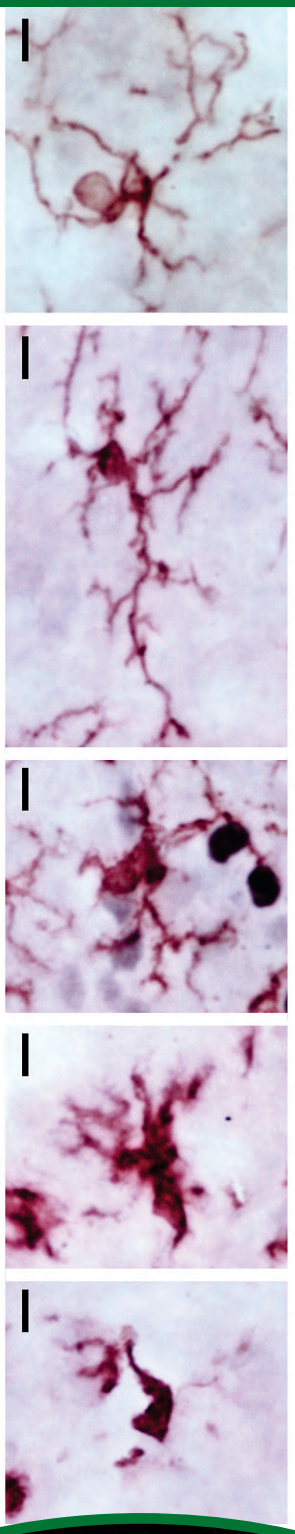
Using an immediate-early gene induction-based functional anatomical mapping strategy, previous work from the Laboratory of Molecular Neuroendocrinology has identified hypothalamic and extended brain circuits that are specifically recruited in response to physiological, psychological and immune stress challenges. They have established the spatial distribution and timing of transcriptional activation of stress-related neuropeptides, corticotropin-releasing hormone (CRH) and vasopressin, and identified the CRH-secreting parvocellular neurons as direct targets of corticosteroid negative feedback. The laboratory has provided ultrastructural and functional evidence for inhibitory GABAergic inputs that impinge upon stress-related CRH neurons and shown its functional plasticity in response to chronic variable stress.
The recent activity in this field involves projects that are aimed at understanding the neuroendocrine and immunological mechanisms which are responsible for chronic stress-induced depression. Our aim is to reveal how chronic stress exposure affects microglia function, neuroinflammation and reorganization of the limbic-hypothalamic neurocircuit in major depression. In addition to central circuits, there are ongoing research projects in the Laboratory that will establish the effects of chronic stress on the gut microbiome, mucosal immunity and gut-brain axis. In collaboration with biochemists, microbiologists and biotechnologists, the laboratory develops various psychosynbiotics.

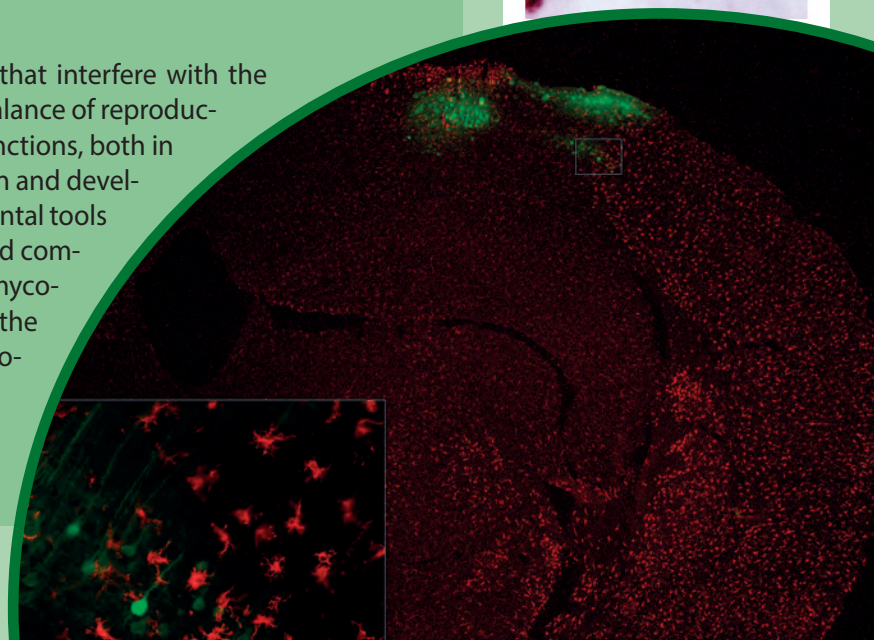
Psychoneurobiology of the Human Stress Response

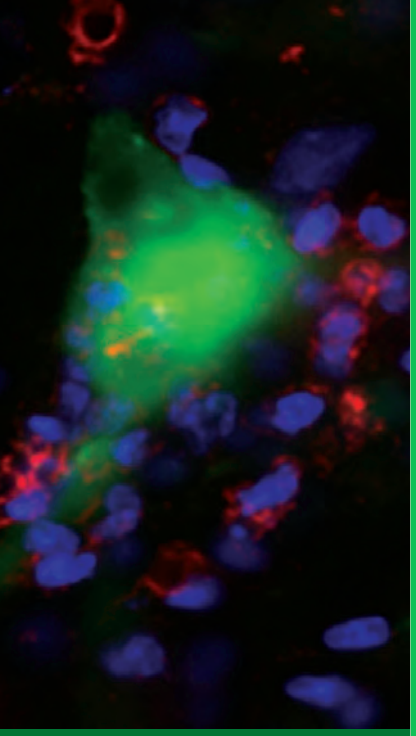
Understanding the neurobiology of stress in humans is far behind that of animal models. The Laboratory of Molecular Neuroendocrinology in collaboration with experts in genetics, psychology, psychiatry and medical technology is currently engaged in a multidisciplinary research program to analyze stress-related brain physiology and pathophysiology. With a combination of high resolution functional brain imaging techniques, autonomic recordings, behavioral analysis, and non-invasive collection of saliva samples for hormone measurement and DNA profiling, these tools are used to measure complex relationships between the recruitment of different brain areas and changes in hormonal, vegetative and behavioral responses, and to correlate these changes with genetic polymorphisms underlying individual responses to stress.

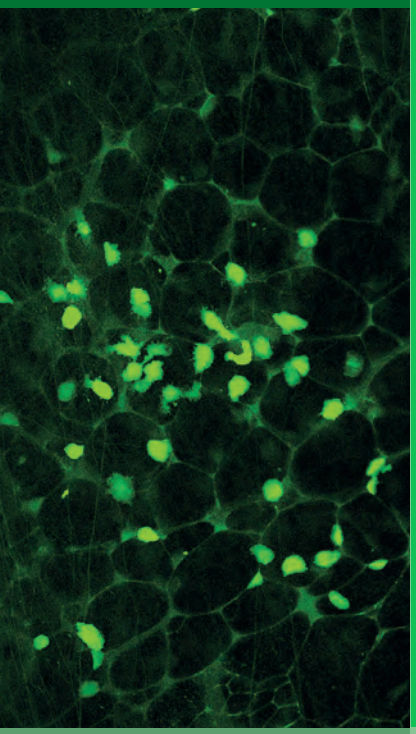
Endocrine Disruptors

Endocrine disruptors are various chemicals that interfere with the host's endocrine system and result in an imbalance of reproductive, metabolic, neurological and immune functions, both in humans and wildlife. In addition to the design and development - *in vivo* and *in vitro*- of new experimental tools with which to analyze the effects of single and complex exposures of the endocrine disruptor mycotoxin zearalenone and the pesticide atrazine, the Laboratory also aims to reveal the neuroendocrine mechanisms through which they act.









Inflammation and Obesity

Metabolic X syndrome is a serious metabolic condition characterized by abdominal obesity, glucose intolerance, insulin resistance, dyslipidemia and high blood pressure. Furthermore, in patients with MX, a low grade subclinical inflammation of the white adipose tissue is recognized. Diet-induced obesity and related peripheral and central inflammation are major risk factors for metabolic, neurological and psychiatric diseases. Recent work from the Laboratory revealed that the chemokine fractalkine (Cx3CL1) and its receptor Cx3CR1 play a pivotal role in recruitment, infiltration and proinflammatory polarization of leukocytes in the white adipose tissue of mice fed with a high fat diet.

Central and Peripheral Inflammation and Cerebrovascular Disease

(Principal Investigator: Ádám Dénes PhD, from 2015 Head of the Laboratory of Neuroimmunology)

Inflammation is a key contributor to cerebrovascular disease. Recent data indicate that both central and systemic inflammatory processes are involved in the development of common brain diseases, such as stroke, schizophrenia, Alzheimer's- or Parkinson's disease and also contribute to worse clinical outcome. Our research aims at investigating mechanisms by which central and systemic inflammation mediate brain injury after stroke. Our data show that rodent models of systemic inflammation (induced by infection, obesity or atherosclerosis) show larger brain injury and worse neurological outcome after experimental stroke, and this can be prevented by blockade of inflammatory processes, such as actions mediated by the key proinflammatory cytokine interleukin 1 (IL-1). Blockade of IL-1 actions, inflammasome-mediated processes and other key proinflammatory mediators also reduces brain injury in mice without any systemic inflammatory burden after experimental stroke, indicating the potential therapeutic value of anti-inflammatory interventions. By using *in vivo* two photon imaging, SPECT/CT imaging, full transcriptome sequencing and transgenic animal models, we aim to understand how early inflamatory actions contribute to blood-brain barrier breakdown and excitotoxicity after acute brain injury. We also study the role of inflammation in the pathophysiology of neonatal asphyxia and central herpes virus infections.

from left: Szilamér Ferenczi, Ádám Dénes, Ágnes Polyák, Krisztina Kovács, Nikolett Lénárt, Zsuzsanna Winkler, Dániel Kuti

Selected publications from the last 10 years:

- Polyak A, Ferenczi S, Denes A, Winkler Z, Kriszt R, Pinter-Kubler B, Kovacs KJ The fractalkine/Cx3CR1 system is implicated in the development of metabolic visceral adipose tissue inflammation in obesity. BRAIN BEHAVIOR AND IMMUNITY (2014)
- Denes A, Pradillo JM, Drake C, Sharp A, Warn P, Murray KN, Rohit B, Dockrell D, Chamberlain J, Casbolt H, Francis S, Martinecz B, Nieswandt B, Rothwell N, Allan SM Streptococcus pneumoniae worsens cerebral ischaemia via IL-1 and platelet GPIbalpha ANNALS OF NEUROLOGY (2014)
- Kovacs KJ CRH: The link between hormonal-, metabolic- and behavioral responses to stress. JOURNAL OF CHEMICAL NEUROANATOMY 54: pp. 25-33. (2013)
- Smith CJ, Lawrence CB, Rodriguez-Grande B, Kovacs KJ, Pradillo JM, Denes A The Immune System in Stroke: Clinical Challenges and Their Translation to Experimental Research JOURNAL OF NEUROIMMUNE PHARMACOLOGY 8:(4) pp. 867-887. (2013)
- Pinter-Kubler B, Ferenczi S, Nunez C, Zelei E, Polyak A, Milanes MV, Kovacs KJ. Differential Changes in Expression of Stress- and Metabolic-Related Neuropeptides in the Rat Hypothalamus during Morphine Dependence and Withdrawal. PLOS ONE 8:(6) p. e67027. (2013)
- Miklós I, Kovács KJ Reorganization of Synaptic Inputs to the Hypothalamic Paraventricular Nucleus During Chronic Psychogenic Stress in Rats BIOLOGICAL PSYCHIATRY 71:(4) pp. 301-308. (2012)
- Kriszt R, Krifaton C, Szoboszlay S, Cserháti M, Kriszt B, Kukolya J, Czéh Á, Fehér-Tóth S, Török L, Szoke Z, Kovács KJ, Barna T, Ferenczi S A New Zearalenone Biodegradation Strategy Using Non-Pathogenic Rhodococcus pyridinivorans K408 Strain PLOS ONE 7:(9) Paper e43608. 9 p. (2012)
- Bajayo A, Bar A, Denes A, Bachar M, Kram V, Attar-Namdar M, Zallone A, Kovacs KJ, Yirmiya R, Bab I Skeletal parasympathetic innervation communicates central IL-1 signals regulating bone mass accrual PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 109:(38) pp. 15455-15460. (2012)
- Denes A, Ferenczi S, Kovacs KJ Systemic inflammatory challenges compromise survival after experimental stroke via augmenting brain inflammation, blood-brain barrier damage and brain oedema independently of infarct size JOURNAL OF NEUROINFLAMMATION 8: p. 164. (2011)
- Ferenczi S, Zelei E, Pinter B, Szoke Z, Kovacs KJ Differential regulation of hypothalamic neuropeptide y hnRNA and mRNA during psychological stress and insulin-induced hypoglycemia MOLECULAR AND CELLULAR ENDOCRINOLOGY 321:(2) pp. 138-145. (2010)