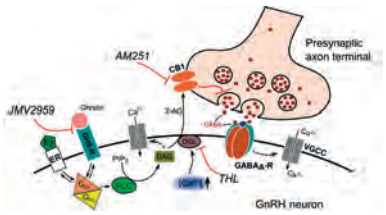
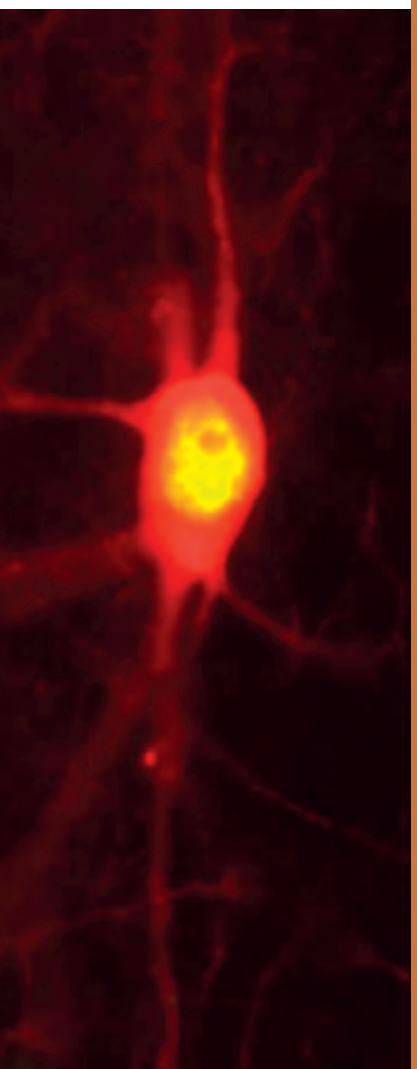
Laboratory of Endocrine Neurobiology

Department of Endocrine Neurobiology

Head of Laboratory:
Zsolt Liposits MD, PhD



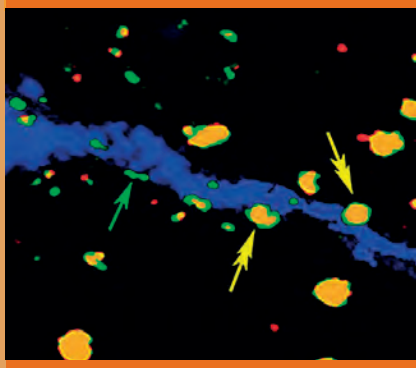


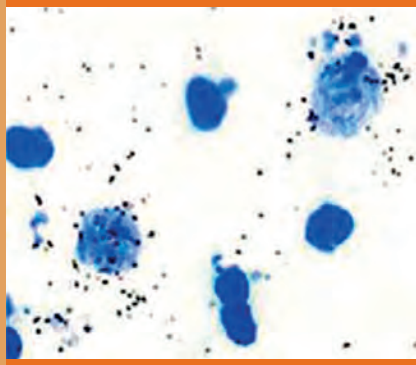
Mission statement

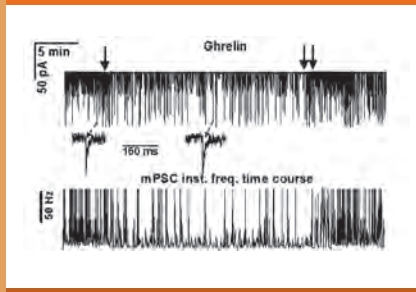
Reproduction, metabolism and adaptation are essential physiological functions of the human body that are regulated by the brain, mainly via the hypothalamus-pituitary-endocrine systems. Dysfunctions of the endocrine axes can result in severe illnesses including infertility, obesity and chronic stress. The prevention and proper medical treatment require the elucidation of central regulatory mechanisms that control the operation of the gonads, the thyroid and adrenal glands. The hypothalamus sends hormonal and neuronal messages to activate endocrine glands and peripheral organs. The communication is reciprocal. The secreted gonadal, thyroid and adrenal hormones report to the brain and the pituitary, in addition to exerting key effects on different peripheral organ systems. In the nervous system, hormone levels are sensed by specific receptors that relay the information to genomic and non-genomic cellular machineries. The hormonal regulation acting upon specific neuronal networks of the brain is manifested in the control of fertility, food intake, energy expenditure, water and salt consumption, adaptation to acute and chronic stress, mood, cognition, memory, sexual and aggressive behaviors. The Laboratory of Endocrine Neurobiology has been engaged to the exploration of the neuronal and hormonal mechanisms that take part in the physiological processes of reproduction, feeding and adaptation. State of the art methodologies are used to achieve these goals including recombinant DNA techniques, microarray, qRT-PCR, immunocytochemistry, *in situ* hybridization, electron microscopy, transgene technologies, fMRI and electrophysiology. The translation of the scientific results contributes to open new avenues in fertility, obesity and mood disorder research fields.

Senior scientists: Imre Farkas PhD, Erik Hrabovszky MD, PhD, Imre Kalló MD, PhD, Miklós Sárvári PhD
Postdoctoral fellow: Csaba Vastagh PhD
Ph.D. students: Zsuzsanna Bardóczi, Katalin Skrapits, Tamás Wilheim
Junior scientists: Csilla Maurnyi, Csilla Molnár
Technicians: Barna László, Hajnalka Bekó
Undergraduate students: Anna Csepregi, Veronika Csillag, Vivien Kanti, Zsófia Mauskopf
Secretary: Márta Turek

Hypothalamic regulatory mechanisms of reproduction





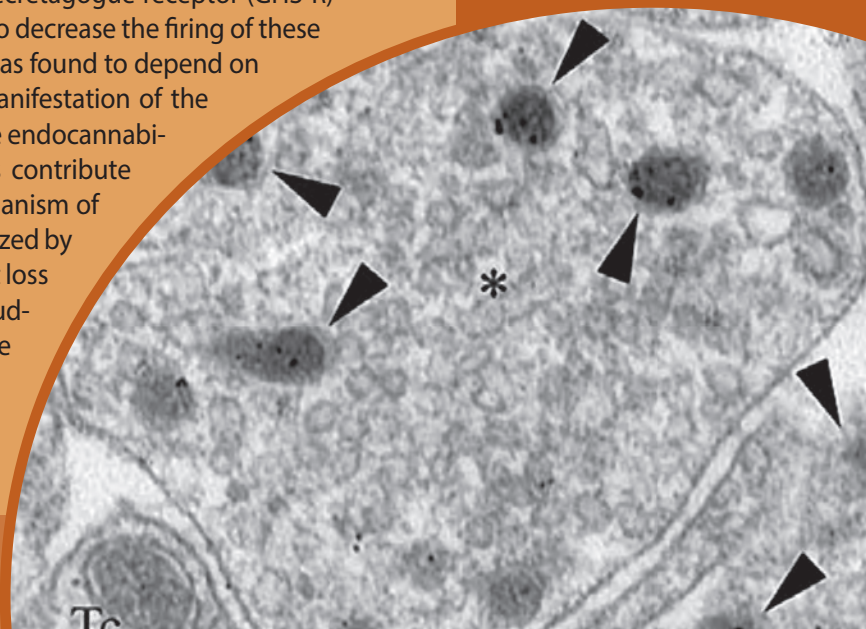


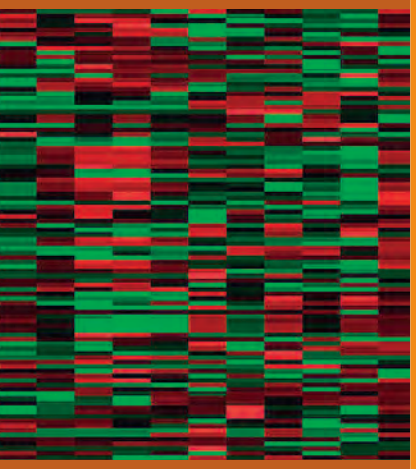
Gonadotropin-releasing hormone (GnRH)-synthesizing neurons represent the final output pathway of the hypothalamus in the neuroendocrine control of reproduction. Pulsatile GnRH secretion into the hypophysial portal circulation regulates the synthesis and release of the two adenohypophysial gonadotropins, LH and FSH, which in turn govern gonadal functions. Gonadal sex steroid hormones exert positive and negative feedback effects on the neurosecretory output of GnRH neurons via mechanisms that are poorly understood. A major research focus of the Laboratory of Endocrine Neurobiology has been on the neuronal and hormonal mechanisms that mediate the effects of 17β-estradiol on GnRH neuronal functions.

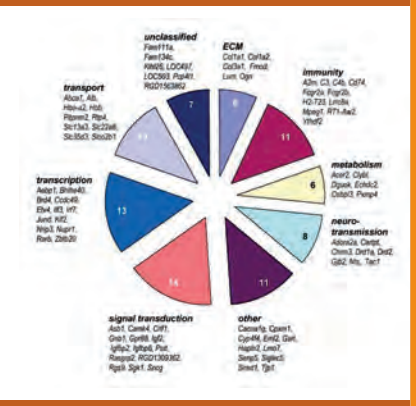
Members of the Laboratory provided the first neuromorphological evidence that, against a long-held view, GnRH neurons do possess receptors to sense circulating estrogen levels. The presence of the beta isoform of the estrogen receptor (ER-β) they observed in GnRH neurons of rats and humans was also found to characterize other hypothalamic systems that lack the classic estrogen receptor (ER-α), including vasopressin and oxytocin neurons of the magnocellular neurosecretory system. A recently revealed feature of GnRH neurons has been their glutamatergic character based on the expression of vesicular glutamate transporter-2 (vGLUT-2) mRNA and protein.

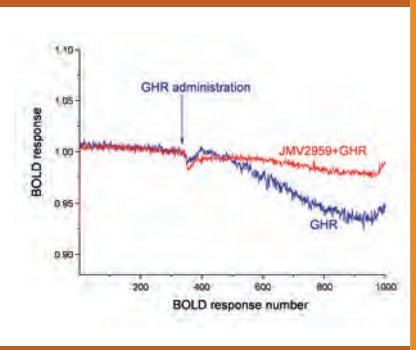
The Laboratory used light- and electron microscopic techniques on rodent and human tissues to reveal novel circuitries that may mediate sex steroid-, circadian-, metabolic- and stress signals to GnRH neurons. The newly-characterized input systems include histaminergic, cholinergic, peptidergic (AGRP/NPY), noradrenergic (DBH/NPY), GABA-ergic and glutamatergic afferents. Recent reports from the Laboratory on the distribution and connectivity to GnRH neurons of kisspeptin-, RF-amide related peptide- and neurokinin B-containing neurons have been of key importance to understand the regulation of the reproductive cycle in the human. It is noteworthy that human basal hypothalamic samples show a low level of overlap between kisspeptin, neurokinin B, and dynorphin immunoreactivities, contrasting and challenging the KNDy neuron concept in rodents. Furthermore, age and gender specific events characterize the expression of kisspeptin and neurokinin B in the human infundibular nucleus.

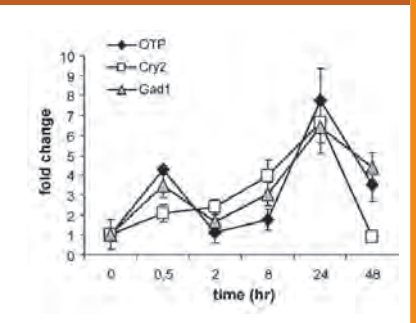
With combined electrophysiological and morphological approaches, the Laboratory has recently clarified a novel mechanism whereby endocannabinoids reduce the excitatory GABA-ergic afferent drive upon GnRH neurons. This may explain the known inhibitory actions of cannabinoids on reproduction. Studying the regulatory effects of the orexigenic hormone, ghrelin, we have revealed the expression of growth hormone secretagogue receptor (GHS-R) in GnRH neurons and the capability of ghrelin to decrease the firing of these neurons. The effectiveness of ghrelin's action was found to depend on the actual estradiol hormone milieu. In the manifestation of the effect of ghrelin, the principal role of retrograde endocannabinoid signaling was elucidated. These findings contribute to the better understanding of the pathomechanism of anorexia nervosa, the mental disease characterized by a high level of circulating ghrelin, severe weight loss and amenorrhea. Recent innovations and studies of the Laboratory have been aimed at the











expression profiling of GnRH neurons in order to discover novel regulatory mechanisms operating in the maintenance of GnRH neuron physiology.

Regulation of cortical functions by estradiol

The sex hormone 17β-estradiol (E2) is primarily synthesized in maturing ovarian follicles. Cyclic changes in serum E2 levels across the menstrual cycle exert profound effects on reproductive tissues in women. E2 also plays an important role in the maintenance of normal limbic and cortical functions. Around menopause, when E2 levels decline, the incidence of cognitive and mood disorders increases, which can be prevented with hormone replacement therapy. A major research interest of the Laboratory has been in the molecular mechanisms whereby E2 preserves good mood, capability of learning and processing memory via interactions with cortical and limbic structures. The classic actions of E2 are mediated by two estrogen receptor isoforms, ERα and ERβ. They are ligand-dependent transcription factors which regulate gene expression in the presence of E2. Prefrontal cortex (PFC) and the hippocampus are known targets of steroid hormone signaling. The Laboratory has studied the genomic responses of the prefrontal cortex and the hippocampus to E2 replacement and treatments with ERα and ERβ selective agonists. Estrogen receptor agonist-regulated genes were identified by microarray technology and selected changes were confirmed by quantitative real-time PCR. Several E2-regulated transcripts were also localized with high-resolution *in situ* hybridization and immunocytochemical techniques.
In the PFC, genomic alterations in response to E2 were partly related to dopaminergic neurotransmission, immune surveillance and transport processes. In the hippocampal formation, ovariectomy and subsequent treatment with estrogen receptor agonists powerfully tuned the innate immune system of middle-aged female rats. Analogous changes were observed in the hippocampus of post-menopausal women. The results shed light on the molecular mechanisms whereby estrogen replacement therapy preserves cortical and limbic functions.

Regulation of limbic functions via the reward system

The reward system of the brain has a major contribution to the modulation of limbic functions including regulation of feeding, adaptation and reproduction. The ventral tegmental area (VTA) of the rostral mesencephalon has a pivotal role in triggering reward actions mainly via dopaminergic, mesolimbic and mesocortical projections. These neuron circuits are also regulated by gonadal steroids and metabolic signals. Recent studies of the Laboratory have made an attempt to elucidate the cooperation of neuronal and hormonal mechanisms that influences the initiation of the reward mechanism. Functional MRI (fMRI) measurements revealed the widespread action of the hunger signal, ghrelin, upon the neuronal networks of the reward system. The modulatory effects of ghrelin signaling have been demonstrated in cholinergic neurons of the latero-dorsal tegmentum and also in the basolateral amygdala.
The fMRI BOLD response evoked by amphetamine in the PFC is estrogen hormone dependent. Tract tracing studies revealed connections established by medial hypothalamic nuclei with the VTA. GABA and glutamate were con-

firmed as major neurotransmitters operating in the communication between the hypothalamus and VTA. The orexinergic input from the lateral hypothalamus to dopaminergic neurons of the VTA has been shown in the *post-mortem* human brain as well.

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Selected publications from the last 10 years:

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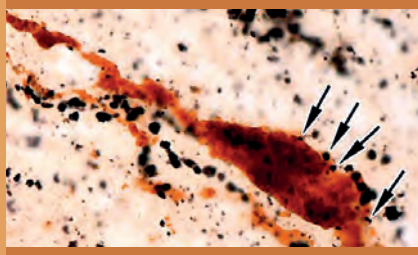

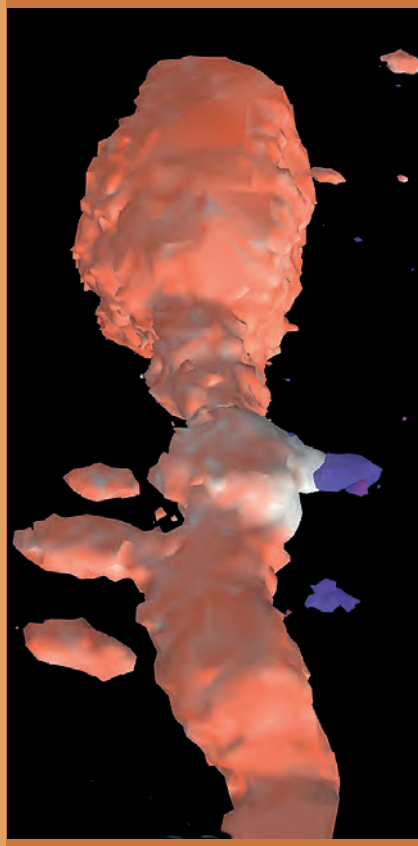

First row, from left: Barna László, Csaba Vastagh, Márta Turek, Miklós Sárvári
Second row: Csilla Molnár, Imre Farkas, Zsuzsanna Bardóczi, Imre Kalló, Flóra Bálint, Katalin Skrapits, Erik Hrabovszky, Tamás Wilheim, Zsolt Liposits