Laboratory of Behavioural and Stress Studies

Department of Behavioural Neurobiology

Head of Laboratory: József Haller, PhD

Mission statement

The group studies the neurobiological background of the stress response and emotional behavior. The approach is biomedical: laboratory models of human disorders are in focus. The main goal is to understand how the stress response develops, how it contributes to the development of behavioral dysfunctions, and how these are controlled by stress-induced changes in neural function. Furthermore, the group is interested in the identification of novel treatment opportunities for the behavioral dysfunctions studied. In order to mimic the clinical problems as closely as possible, several new behavioral models were developed. The main focus is on anxiety, depression and aggression. The goal of such studies is the identification of the complex interaction between the type of stressors and the type of the resulting behavioral dysfunctions. Research performed by the group is multidisciplinary. Endocrinological techniques are employed to characterize the hormonal consequences of stressors and their correlation with behavioral effects. Stress-induced changes in autonomic arousal and its correlation with behavioral dysfunctions is studied by *in vivo* biotelemetry. Brain mechanisms are studied by behavioral pharmacological, immunocytochemical, and recently, by optogenetic and epigenetic techniques. Finally, the possibilities of pharmacological intervention are explored by behavioral pharmacological studies that are based on the locally-discovered neural correlates and mechanisms that underlie stress-induced behavioral dysfunctions. The group is involved in drug development programs initiated locally or performed on request by pharmaceutical companies.

A mouse explores one of the compartments of the place-preference box, which is used to investigate the rewarding or aversive nature of drugs. Note that each compartment is marked differently to easy their recognition by experimental subjects.

Senior scientists: Manó Aliczki, PhD; Eszter Bodóné Sipos, PhD; Kornél Demeter, PhD; Éva Mikics, PhD; Máté Tóth, PhD; Dóra Zelena, MD, PhD
Ph.D. students: Diána Balázsfi, Anna Fodor, László Biró, Zoltán Balogh
Graduate research assistant: Lívia Farkas
Undergraduate research assistants: Bíborka Bruzsik, Péter Csikota, Áron Kerényi, Christina Miskolczi, Pál Pottyondy, Tamás Szabó, László Szente, Bibiána Török, Eszter Urbán
Technicians: Katalin Gyimesiné Pelczer, Beáta Barsvári
Research advisors: István Barna, Gábor Makara, MD, PhD

Studies on aggression

Studying aggression is one of the long-standing interests of the group. Its unique contribution to this field is the discovery that etiological factors of aggression-related human psychopathologies induce abnormal forms of aggression in laboratory rodents. The theoretical bases of this new approach in aggression research were laid down in cooperation with MR Kruk (University of Leiden, the Netherlands) (Haller and Kruk, 2006), and was recently amended in cooperation with scientists from Tufts University, and the University of Groeningen (Miczek, de Boer and Haller, 2013). Recently, the group together with scientists from the UK, Switzerland, and Germany proposed that such models may be used to study the impact of early-life stressors on the development of antisocial behavior (Haller et al., J Neuroendocrinol, 2014). Based on initial findings (Mikics et al., 2004) and the principles established later on, the group developed two models of abnormal aggression, one for psychopathologies characterized by instrumental/proactive and another for disorders differentiated by emotional/reactive aggression (e.g. antisocial personality disorder and intermittent explosive disorder, respectively).
The second discovery of the group is that the neural underpinnings of abnormal aggression are largely etiological factor- and emotionality-dependent (Tulogdi et al., 2010; Tóth et al., 2012), revealing that there are multiple neurobehavioral "roads" to abnormal aggression a finding to be considered when novel treatment options for aggression-related psychopathologies are evaluated. At present, the group studies the developmental mechanisms that lead to the emergence of etiological factor-dependent brain alterations and the details of aggression-related neural communication by epigenetic and optogenetic techniques, respectively.

Endocannabinoids, stress and behavior

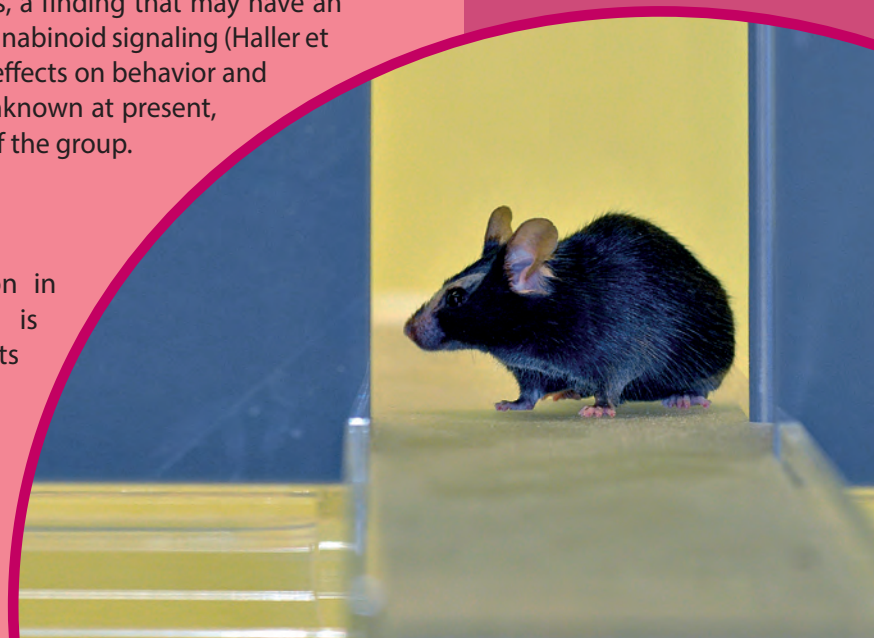
By using transgenic animals, this group was the first to establish a direct link between cannabinoid CB1 receptors and anxiety. Subsequent research involving the administration of stressors concomitantly with behavioral testing revealed that the role of cannabinoids is more complex than previously thought. The first publication on the issue demonstrated that the effects of cannabinoid agents largely depend on how aversive the testing environment is; moreover, cannabinoid effects are sometimes opposite depending on testing conditions (Haller et al., 2009). More recent findings of the group show that endocannabinoid signaling has a large impact on the way in which an individual copes with stress, a finding that may have an impact on the therapeutic implications of cannabinoid signaling (Haller et al., 2014). The relationship between specific effects on behavior and general effects on stress-coping is largely unknown at present, and constitutes one of the research targets of the group.

Vasopressin, stress and behavior

The role of vasopressin neurotransmission in stress responses and behavioral control is among the long-standing scientific interests

A mouse pokes his nose in one of the holes of the operant learning apparatus. Operant learning is frequently used to investigate the effects of environmental stressors, genetic influences and drugs on cognition, e.g. learning and memory as well as cognitive flexibility.

A mouse standing in the central area of the of the elevated plus-maze apparatus, which is frequently used to investigate anxiety states.



The three-chamber social interaction box is used to investigate social motivation, partner preference and social recognition. The subject is placed in the middle chamber; time spent in the two adjacent chambers, which may be left empty or may host familiar or unfamiliar individuals provides important information on the social behavior of subjects.

The recording of heart rates, body temperature, and locomotion by in vivo biotelemetry. Upper panell: on-line signals; lower panel: numeric values.

of the group. By studying the vasopressin-deficient Brattleboro rat, the group showed that vasopressin neurotransmission affects the development of the organism; this peptide is the primary secretagogue of the hypophyseal component of the stress-response in pups, and contributes to the development of anxiety and depression in newborn and adult rats. Recently, the group showed for the first time that vasopressin promotes maternal behavior in lactating dams, surprisingly in conjunction with contributing to the development of depression-like symptoms; the neural underpinnings of these roles were also investigated (Fodor et al., 2012). The group also revealed that in contrast to adults, the mineralocorticoid aldosterone is the main stress-responsive adrenocortical hormone in pups (Varga et al., 2013). Together with their earlier findings on age-related changes in central stress-controlling mechanisms, these findings show that the neuroendocrine stress response is specific in newborns. The developmental implications of this phenomenon are currently under study.

Emerging research areas

Within a consortium involving several groups of the Institute, the laboratory is engaged in optogenetic studies into the behavioral roles of the median raphe, a major source of cortical serotonergic innervation. In contrast to the dorsal raphe, neurons of this nucleus preferentially establish synaptic contacts with target neurons whose behavioral and physiological roles are largely unknown. They focus on anxiety and learning.
Prompted by earlier interest in conditioned fear (Mikics et al., 2008), the group initiated studies into the roles of glutamate receptor subtypes in mediating trauma-induced behavioral dysfunctions. By scrutinizing molecular details of glutamatergic neurotransmission, these studies have the potential of unraveling novel treatment options for post-traumatic stress disorder.

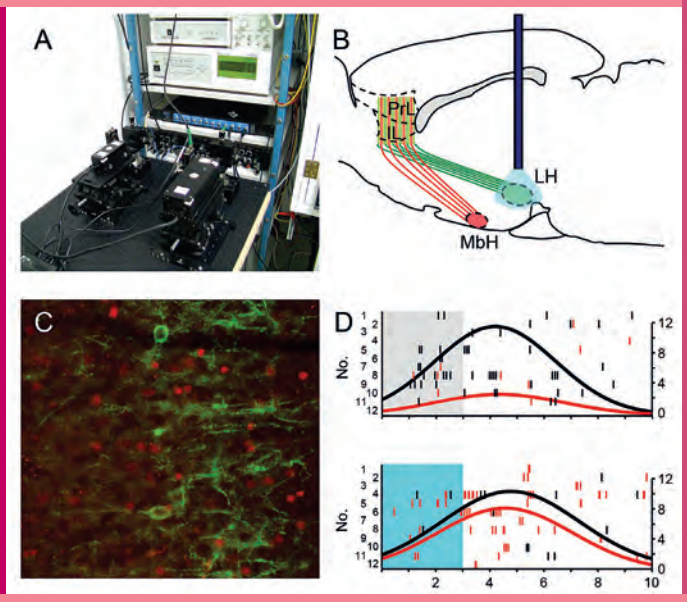
Selected publications from the last 10 years:

- Haller J., Kruk M. R. Normal and abnormal aggression: human disorders and novel laboratory models. Neurosci Biobehav Rev 2006; 30: 292-303.
- Miczek K. A., de Boer S. F., Haller J. Excessive aggression as model of violence: a critical evaluation of current preclinical methods. Psychopharmacology 2013; 226: 445-458.
- Mikics E., Kruk M. R., Haller J. Genomic and non-genomic effects of glucocorticoids on aggressive behaviour in male rats. Psychoneuroendocrinology 2004; 29: 618-635.
- Tulogdi A., Toth M., Halasz J., Mikics E., Fuzesi T., Haller J. Brain mechanisms involved in predatory aggression are activated in a laboratory model of violent intra-specific aggression. Eur J Neurosci. 2010; 32: 1744-1753.
- Toth M., Tulogdi A., Biro L., Soros P., Mikics E., Haller J. The neural background of hyper-emotional aggression induced by post-weaning social isolation. Behav Brain Res. 2012; 233: 120-129.
- Haller J., Barna I., Barsvari B., Gyimesi Pelczer K., Yasar S., Panlilio LV., Goldberg S. Interactions between environmental aversiveness and the

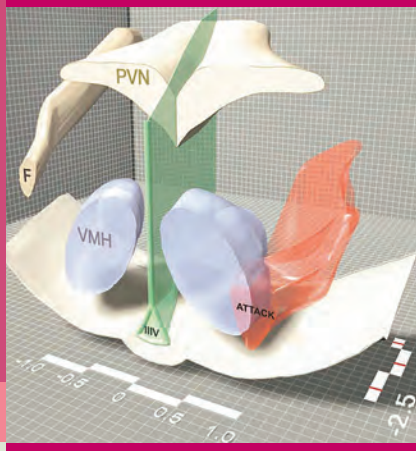
anxiolytic effects of enhanced cannabinoid signaling by FAAH inhibition in rats. Psychopharmacology 2009; 204: 607-616.

- Haller J., Aliczki M., Pelczer K. G., Spitzer K., Balogh Z., Kantor S. Effects of the fatty acid amide hydrolase inhibitor URB597 on coping behavior under challenging conditions in mice. Psychopharmacology 2014; 231: 593-601.
- Fodor A., Klausz B., Pintér O., Daviu N., Rabasa C., Rotllant D., Balazsfi D., Kovacs K. B., Nadal R., Zelena D. Maternal neglect with reduced depressive-like behavior and blunted c-fos activation in Brattleboro mothers, the role of central vasopressin. Horm Behav. 2012; 62: 539-551.
- Varga J., Ferenczi S., Kovács K. J., Garafova A., Jezova D., Zelena D. Comparison of stress-induced changes in adults and pups: is aldosterone the main adrenocortical stress hormone during the perinatal period in rats? PLoS One. 2013; 8: e72313.
- Mikics E., Tóth M., Varjú P., Gereben B., Liposits Z., Ashaber M., Halász J., Barna I., Farkas I., Haller J. Lasting changes in social behavior and amygdala function following traumatic experience induced by a single series of foot-shocks. Psychoneuroendocrinology. 2008; 33: 1198-1210.

Maternal behavior is studied in conjunction with stress responses in the vasopressin-deficient Brattleboro rat.



Optogenetic experiments in a nutshell. *A*, The photostimulator producing laser light of specific wavelength; *B*, A graph showing the main features of an experimental design; *C*, Microscopic image showing the investigated neurons; *D*, Some of the results revealing the role of particular neural projections in the control of aggression.



A three-dimensional reconstruction of the hypothalamic attack area, a brain structure from where attacks on conspecifics can rapidly and reliably be elicited by electrical stimulation. The figure was published by the Behavioral Neurobiology department and by Dr. Menny R. Kruk from the Leiden University, The Netherlands. Abbreviations: attack; the hypothalamic attack area; F, fornix; IIIV, third ventricle; PVN, paraventricular nucleus of the hypothalamus; VMH, ventromedial nucleus of the hypothalamus. The scales show distance from Bregma (mm).

Back row, from left: Kornél Demeter, László Bíró, Eszter Sipos, Dóra Zelena, János Varga, Máté Tóth, József Haller
Front row: Beáta Barsvári, Lívia Farkas, Diána Balázsfi, Anna Fodor, Éva Mikics, Manó Alicki, Katalin Gyimesiné Pelczer