Doctoral School of Basic Medical Sciences

HOMEOSTATIC AND BEHAVIORAL EFFECTS OF INTERLEUKIN-1β MICROINJECTION INTO THE CINGULATE CORTEX

Ph.D. Thesis

Bettina Réka László

Tutor: Zoltán Karádi M.D., Ph.D.

Head of the PhD Program: Zoltán Karádi M.D., Ph.D.

Head of the Doctoral School: Júlia Szekeres M.D., Ph.D., D.Sc.

University of Pécs,

Medical School,

Institute of Physiology

Pécs, 2020

I. Introduction

Nutritional and metabolic illnesses, like diabetes mellitus, anorexia and bulimia nervosa, metabolic syndrome, obesity, etc. are public diseases in which a great proportion of the society is affected and, in most cases, the treatment is symptomatic, i.e., limited only to the elimination or, at least, weakening of the pathologic symptoms. With respect to the unsolved problem of the lack of causal therapy in this field, it is important to note that research of our laboratory is greatly determined by the hypothesis that – in addition to the obvious peripheral deficits – the main causal factors in the background of these illnesses are the various kinds of disturbances of the central control mechanisms which get manifested as the consequence of usually discret regulatory deficits, a kind of functional imbalances, rather than morphological malformation. Homeostasis, that is, the adaptive control of the maintenance of the inner balance of the organism, is based on the integration of the above peripheral and central mechanisms by complex neurochemical, endocrinological and immunological processes in which the cellular communication is accomplished, at least partly, by cytokines. The investigation of related cytokine mediated central regulatory processes is in the focus of our present study. The role of primary cytokine interleukin-1β (IL-1β) in feeding behavior associated complex neural and humoral regulatory processes has long been reported in literature. Its food intake decreasing [1-3], water intake affecting [1, 4] and body temperature increasing effects [1, 4-8] are well known. Its role has also been examined in glucose homeostasis [9, 10] and its effect on the plasma levels of other metabolites has also been shown [11, 12]. Furthermore, there is an increasing amount of data that proves connection between IL-1 related inflammatory states and the disorders of the taste system and accompanying illnesses [13-18]. In our present study, effect of IL-1β on feeding and metabolic processes, body temperature and nutrition associated behavioral and learning mechanisms have been examined after the cytokine microinjection into the anterior cingulate cortex (ACC). The activation of this cortical region has been shown in processes affecting the maintenance of the homeostasis: hunger [19], thirst [20], or hypoglycemia [21], and its role is also known in feeding related motivational processes [22, 23] and the evaluation of relevant stimuli like taste, smell and texture [24-26]. In addition to the above mentioned investigations, we also examined the role of cyclooxygenase (COX) mediated processes in the mechanism of action of the IL-1β, the effect of the cytokine on general locomotor activity of the animals and its possible negative or positive reinforcing capabilities.

II. Objectives

I. In our examinations related to elucidating the homeostatic significance of cingulate cortical IL-1β, we aimed to reveal its effect on the

1. food intake,
2. water intake and
3. body temperature of the animals, and
4. we also investigated whether the COX inhibitor paracetamol alters these effects of the cytokine.

II. In our metabolic experiments we examined the effect of cingulate cortical IL-1β microinjection on the

1. blood glucose level and
2. plasma levels of relevant metabolites (total cholesterol, triglyceride, HDL, LDH, uric acid) of the rats.

III. In our investigations related to the feeding behavior of the animals, we aimed to explore whether IL-1β microinjection into the ACC

1. causes taste perception alterations in taste reactivity test,
2. can induce conditioned taste aversion,
3. can modify conditioned taste aversion induced by lithium-chloride.

IV. In our general behavioral experiments we examined whether cingulate cortical IL-1β

1. affects the locomotor activity (distance moved, number of crossings, time spent in the distinct areas of the experimental apparatus), and species-specific stereotypical movement patterns (rearing, grooming, sniffing) of the rats (open field test),
2. can exert negative or positive reinforcing effect (conditioned place preference test).

III. Materials and methods

1. Subjects

Altogether 280 adult male Wistar rats were used in this series of experiments. The animals were kept on standard laboratory chow pellet food (Charles River Ltd., Budapest, Hungary) and tap water ad lib in individual cages in a room with constant temperature (23 ± 2 °C) and humidity (55-60%), as well as with 12-12 hours dark/light cycle. Our experiments were performed in accordance with institutional (breeding license No.: BA 02/2000-72/2017), national (Law XXVIII, 1998, Government Decree, 40/2013. (II.14) Hungary) and international regulations (European Community Council Directive 86/609/EEC; 1986, 2006; European Directive 2010/63/EU of the European Parliament and of the Council; National Institutes of Health Guidelines, 1997). The number of animals minimally needed to evaluate the results was used in our experiments and all efforts were made to provide the required environmental and social conditions for their well-being, and also, to minimize their suffering.

2. Surgery

Guide cannulas for the intracerebral IL-1β or vehicle microinjections were compiled from stainless steel hypodermic needles (23 G). These microcannulas were implanted bilaterally above the cingulate cortex in stereotaxic operation sessions. During the microinjection session, *delivery cannulas* were passed through these guide cannulas to administer substances directly into the cingulate cortex.

The surgery was performed after a 10-14 days adaptation period of the animals, during which their body weight was constantly monitored. The operation was carried out under anesthesia introduced by the intraperitoneal injection of 4:1 mixture of ketamine (Calypsol, Richter Gedeon Rt., Hungary; 80 mg/kg body weight) and diazepam (Seduxen, Richter Gedeon Rt., Hungary; 20 mg/kg body weight). After the head of the animals was fixed, a longitudinal incision was made above the scalp and the bone was cleared. Hydrogen peroxide was used to reduce bleeding and for disinfectioning as well. Under microscopic control, a stereotaxically oriented hole was drilled through the skull by means of an appropriate dental drill. Guide cannulas were placed on the surface of the dura above the cingulate cortex through this hole by means of a micromanipulator (MN-33 Narishige, Japan). Coordinates (AP: B + 2.7 mm, ML:

0,9 mm) were determined by using the rat brain atlas of Paxinos and Watson [36]. Pairs of the cannulas were fixed in position with dental acrylic, then, after local application of antiseptic powder (Tetran, Richter Gedeon Rt., Hungary), the wound was closed. The operations were followed by one week of recovery period, during which the condition of the animals was constantly monitored. In the first three days (or longer if necessary) analgesia was used (Meloxidyl 5 mg/ml; 1 mg/kg sc.).

Chronic intraoral, so called *taste cannulas* made of polyethylene tubes (HIBIKI, Japan; outer diameter: 1.33 mm) were also implanted into the oral cavity of the animals taking part in the taste reactivity test. These operations were performed right before the previously mentioned guide cannula implantation, in joint sessions, under the same anesthesia, in order to reduce the inconveniences caused by the surgery. These cannulas were used to deliver the gustatory stimulus solutions into the mouth during the test. They were placed anterolateral to the first maxillary molar and led through a small transbuccal slit subcutaneously up to the lateral part of the skull. Cannulas were fixed by surgical stitches, and antiseptic solution was applied locally after finishing this operation (Betadine, EGIS, Budapest, Hungary). The cannulas were inspected every day till the test, rinsing them was also useful to accustom the animals to the experimental circumstances.

3. Microinjection

The microinjections were performed in well-handled awake animals after one week of recovery period following the operations. The rats were divided into two or four groups, depending on the experiment (in case of food and water intake and body temperature measurements, paracetamol pretreatment was also used additionally). The following groups, with the same mean body weight, were used in these experiments:

- IL-1β (Sigma-Aldrich, I2393; 5 ng/µl; dissolved in 0.1% phosphate buffer saline /PBS/ containing 0.1% bovin serum albumin /BSA/) treated;
- sterile PBS treated, control;
- paracetamol (UP MS Pharmacy, 15 µg/µl, dissolved in sterile PBS) + IL-1β microinjected;
- paracetamol + sterile PBS treated.

Substances were administered into the cingulate cortex as bilateral microinjections by means of a microinfusion pump (Cole Parmer 789200C). Hamilton syringes containing the solutions were connected to the stainless steel ***delivery cannulas*** (30 G) via Hibiki 3 (Hibiki, Japan) polyethylene tubes. The delivery cannulas were then passed on to the required brain area, i.e., to the ACC (AP: Bregma + 2.7 mm, ML: 0.9 mm, V: 1.6 mm) through the previously implanted guide cannulas. During the 1 minute interval of the microinjection, 0.75 µl solution (that means, 3.75 ng of IL-1β) was given each side of the brain. After the administrations were finished, the cannulas were left in place in the brain for an additional minute to allow free diffusion of chemicals and to prevent backflow of the solutions. Paracetamol pretreatment was performed 25 minutes before the IL-1β or PBS administration, also as a bilateral microinjection.

4. Experiments

4.1. Food and water intake

Four groups of rats were formed in these experiments: both the cytokine-treated and the control animals were divided into two further groups and half of these animals received paracetamol pretreatment 25 minutes before the administration of IL-1β or PBS.

Food and water intake measurements were performed after 24 hours of food deprivation. Laboratory chow food was given back to the animals after the microinjections at 6 pm (the beginning of the active period of the rats). The short- (2 h, at 8 pm), medium- (12 h, at 6 am) and long-term (24 h, at 6 pm) food and water intakes were measured to the nearest grams. As preliminary control measurements, food and water consumptions were monitored for several days (at identical times of the day) before the treatment day.

4.2 Body temperature

Body temperature (BT) was determined rectally, by means of a digital thermometer with the accuracy of one tenth of centigrade (°C). The measurement was performed just before the microinjections and 2 hours later (8 pm) in the previously mentioned four groups. Control measurements were performed for several days (at identical times of the day) before the treatment day.

4.3. Glucose tolerance test

Blood glucose levels (BGL) of the animals were examined in a standardized glucose tolerance test after 12 hours of food deprivation. At the beginning of the study, a control GTT was performed in order to exclude animals with metabolic abnormalities. Intraperitoneal injection of 20% D-glucose solution (0,2 g/100 g bw/ml) was administered i.p., 20 minutes after the IL-1β or PBS microinjections. Blood glucose levels were measured right before the cerebral microinjections and 9, 18, 30, 60 and 120 minutes after the sugar load. Samples were obtained from the tail vein of the rats and BGLs were determined electrochemically by means of a semi-automatic glucometer (Dcont Ideál, 77 Elektronika Kft., Hungary).

4.4. Plasma metabolites

Relevant plasma metabolites (total cholesterol, HDL, LDH, triglycerides, uric acid) were determined after 12 hours of food deprivation. Blood samples were obtained after decapitation of the rats 20 minutes following the IL-1β or PBS microinjections, and were examined with a cold chemistry photometer (Spotchem EZ SP4430, Arkray, Japan).

4.5. Taste reactivity test

An adapted and modified version of the taste reactivity test originally introduced by Grill and Norgren [27] was used in our laboratory. Three days after the surgery, rats were started to be trained to get accustomed to the experimental circumstances. They were placed in a plexiglass cylinder (30 cm high and 30 cm in diameter) for one minute and the taste cannulas were rinsed with distilled water on a daily basis. The taste reactivity tests were started 20 minutes after the intracerebral microinjections: 0.5 ml of the taste solutions were delivered into the oral cavity of the animals at 0.5 ml/min rate by means of a microinjection pump (Cole Parmer 789200C). Gustatory stimulus solutions representing the five basic taste qualities were administered in two concentrations: sweet (sucrose, 0.05 and 0.5 M); salty (NaCl, 0.05 and 0.5 M); sour (HCl, 0.03 and 0.3 M), bitter (quinine-HCl /QHCl/, 0.03 and 3.0 mM); and umami (monosodium-l-glutamate /MSG/, 0.05 and 0.5 M). Species specific facial expressions and postural-locomotor behavioral patterns of animals in response to the taste stimuli were recorded by digital video camera for later frame-by-frame evaluation. A mirror tilted and positioned in 45° angle was fixed under the cylinder, and this enabled the observation of the mouth and the perioral region of the animals during the entire test period. Rhythmic mouth movements,

rhythmic tongue protrusions along the midline, lateral tongue movements and paw licking were evaluated as ingestive, while gaping, chin rubbing, head shaking, forelimb flailing and evoked, escape-like locomotor movements as aversive behavioral patterns. The recordings were analyzed by three experienced evaluators who did not know the grouping of the rats. Responses of the animals, corresponding to the strength and duration of ingestive and/or aversive behavioral patterns, separately, were evaluated by a score (up to 3) for each taste solution. Then, so called ingestive and aversive taste reactivity indices were generated to all the tastes from the average of the summarized scores of the animals by dividing these values by 3.

4.6. Conditioned taste aversion

Conditioned taste aversion (CTA) means the long term avoidance of a certain taste of food or fluid after it is associated with gastrointestinal discomfort or malaise. Two distinct arrangements of the experiment were performed in our present study using different animal groups. On the one hand, the potential taste aversion eliciting capacity of IL-1β itself was tested (1st paradigm). On the other hand, the potential modifying effect of IL-1β on the acquisition process of LiCl induced taste aversion was also examined (2nd paradigm).

Rats were trained to consume their daily water need restricted to 30 minutes intake sessions every morning from 10:00 to 10:30 a.m. The guide cannula implanting surgery took place after the animals had learned the new drinking schedule. After the operations, during 3 days of recovery, water was provided ad libitum for them. Following this 3-day long period, rats were re-accustomed to the daily 30 min fluid consumption schedule. On the conditioning day, a novel taste solution (0.1% Na-saccharinate solution) was introduced to the animals, instead of water.

In the first paradigm, microinjection of IL-1β or PBS (controls) was performed 30 minutes after the fluid consumption session of the animals. In the second paradigm, microinjection of IL-1β or PBS was performed right after the drinking period, and 15 minutes later the rats were injected i.p. with the gastrointestinal discomfort inducing lithium chloride (0.15 M, 20 ml/kg b. w.). After these procedures, animals had water available for 3 days in the 30 minutes schedule again. On the 4th (test) day, water was replaced by saccharin solution again in the ordinary half hour drinking period, and consumptions of the saccharin solution measured on the conditioning and the test days in the cytokine treated and the control groups were statistically compared.

4.7. Open field test

Species specific motor patterns and locomotor activity of the animals were examined in open field test (OPF). On the first day a habituation session was accomplished, and on the second day, basal activity was studied without any microinjections. On the test day, OPF was performed 20 minutes after the bilateral intracerebral microinjections of either the cytokine or the vehicles. The animals were placed into a 50 cm x 50 cm x 50 cm box lit by a red bulb and their activity was recorded for 5 min by means of a digital video camera fixed above the apparatus. The ground of the cage was virtually divided into 16 identical squares in order to define the peripheral, corner and center areas of the box. Rearing, grooming, sniffing, urination and defecation, the distance moved, the number of crossings and the time spent in the different parts of the box were investigated. Data were stored and analyzed by means of the Noldus EthoVision Basic software (Noldus Information Technology B.V., Wageningen, The Netherlands).

4.8. Conditioned place preference test

Positive or negative reinforcing effects of drugs can be examined by the conditioned place preference test [28-30] . Experiments were performed in an isolated experimental room that was dimly lit. The corral consisted of a circular open field arena with a diameter of 85 cm and with a 40 cm high wall. The ground base of the apparatus was divided into four quadrants of equal size by black lines. External visual cues on the inside walls of the corral helped the animals in spatial orientation inside the apparatus. The place preference procedure consisted of a habituation (day 1), a conditioning (day 2) and a test (day 3) trial, each lasted for 900 s (15 min). In the habituation trial animals were placed into the apparatus and had free access to all parts of it for 900 s. The apparatus was cleaned and dried after each rats. The time the animals spent in each of the four quadrants was measured and it was verified that neither place preference, nor place aversion was shown in any of them. After this, the treatment quadrant was determined randomly. On the conditioning day, animals received the IL-1β or PBS microinjections and 20 min later they were restricted to the treatment quadrant for 15 min by means of a plexiglass barrier. On the test day, rats had free access to all parts of the apparatus again. The time they had spent in each of the four quadrants was measured and compared between the two groups. Behavior of the animals was recorded by a digital video camera. Data

were stored and analyzed by means of the EthoVision Basic software (Noldus Information Technology B.V., Wageningen, The Netherlands).

5. Histology, data processing

Histological examinations were performed in order to determine the precise location of the bilaterally positioned cannulas in the brain. After all experiments ended, rats were over-anesthetised (urethane, 40% fresh solution, 1.4g/kg b.w.; i.p.) and transcardially perfused by physiological saline and 10% formaline. Brains were removed from the skull, and fixed in 4% formaline. Frozen, 40 μm thin sections were stained by cresyl violet (Nissl staining). Rats with inappropriate cannula positions (32 animals) were excluded from data analysis. Counting the animals excluded because of other reasons (illness, abscess around the taste cannula, freezing) as well, the results of altogether 221 rats were evaluated.

For the processing and statistical analysis of our experimental data, the "SPSS for Windows" program package was employed. Results were presented as means ± SEM. One-way analysis of variance (ANOVA) followed by Tukey's test for post hoc comparisons or Student's independent samples *t*-test were used for the statistical evaluation of data. Differences were considered to be significant at the level of $p<0.05$.

IV. Results

1. Food and water intake

The results of our food and water intake measurements show that the bilateral microinjection of IL-1β into the cingulate cortex did not cause remarkable alterations in the food and water intakes of the animals. Results did not differ significantly between the cytokine treated and the control groups in any of the measurement dates (2h, 12h, 24h).

2. Body temperature

Body temperature of the animals showed significant elevation after the cingulate cortical microinjection of IL-1β, two hours after the drug administration ($p<0.001$). The paracetamol pretreatment prevented this significant elevation caused by IL-1β. Paracetamol itself and PBS did not cause notable alterations in the body temperature of the rats.

3. Glucose tolerance test

Blood glucose levels of the IL-1β treated animals during the glucose tolerance test showed a tendency toward the higher values compared to the control group and the peak of the curve appeared at a different measurement point (30^{th} minute after the sugar load in case of the control animals, 18^{th} minute in case of the cytokine treated group). In spite of this obvious divergence in the dynamics of the two curves, there were no significant differences between the blood glucose values of the IL-1β treated and the control animals.

4. Plasma metabolites

There was a decrease in the HDL and total cholesterol levels of the cytokine treated animals and these alterations proved to be significant (HDL: $p<0.001$; total cholesterol: $p<0.005$). In the levels of the other examined metabolites (LDH, triglycerides, uric acid), no significant changes were shown between the IL-1β treated and the control groups.

5. Taste reactivity test

The ratio of ingestive and aversive reactions changed in response to three taste solutions. There was no remarkable difference between the ingestive and aversive responses in case of the *lower concentration QHCl* solution in the control group, however, IL-1β treated animals evaluated this taste definitely as an ingestive stimulus ($p<0.001$). The *higher concentration sucrose* solution was clearly pleasant for the control animals: the rate of ingestive responses was significantly higher compared to the aversive ones ($p<0.001$). This significant difference was however not seen in case of the IL-1β treated rats. Similar to the lower concentration QHCl solution, ingestive and aversive reactions in response to the *higher concentration MSG* solution did not differ notably in the control group, the cytokine treated rats however showed significantly more ingestive than aversive responses ($p<0.001$) in case of this taste, that is, they evaluated it definitely as a pleasant stimulus. There were no significant differences between the IL-1β treated and the control animals related to the other taste solutions: 0.05 M NaCl, 0.05 M sucrose, 0.05 M MSG and 0.03 M HCl proved to be clearly pleasant, 3 mM QHCl and 0.3 M HCl proved to be definitely unpleasant for both the control and the cytokine treated animals. Ingestive responses were dominant in both groups, but the difference was not significant in case of the 0.5 M NaCl solution.

6. Conditioned taste aversion

In the first paradigm of the CTA test, IL-1β treatment did not lead to the development of taste aversion: there was no significant difference neither between the fluid consumptions of the IL-1β treated animals on the conditioning and the test days, nor between the fluid consumptions of the control and cytokine treated animals on the test day.

In the second paradigm, IL-1β did not modified the LiCl-induced taste aversion: taste aversion developed in both groups after the ip. injection of LiCl. Fluid consumption values were significantly lower on the test day compared to the conditioning day both in the cytokine treated ($p<0.001$) and the control groups ($p=0.001$). There was no significant difference between the two groups on the test day.

7. Open field test

Significant differences were found between the IL-1β treated and the control groups during the open field test. Number of rearing ($p<0.005$) and grooming ($p<0.05$), distance moved ($p<0.05$) and number of crossings in the corners ($p<0.05$) were significantly higher in case of the IL-1β treated rats. During the habituation and the measurement of the basal activity, there was no remarkable difference in the locomotor activity of the animals. There was no significant difference between the groups related to sniffing, number of crossings in the middle and peripheral parts, and time spent in the different parts of the apparatus.

8. Conditioned place preference test

In the CPP test, no significant differences were found between the groups on the test day. Results of the IL-1β treated animals between the habituation and the test days also did not differ notably. Our results show that neither conditioned place preference, nor conditioned place aversion developed as a result of the cytokine treatment.

V. Discussion

1. Food and water intake

Anorexigenic effect of both peripherally and centrally (icv. and intracerebrally) administered IL-1β has been proved by numerous studies in the last decades [1-4, 6, 8]. In our present study, bilaterally injected IL-1β into the ACC did not exert anorexigenic effect and there was no significant alteration in the water intake of the animals either. Our results show that cingulate cortical IL-1β mediated processes do not take part in the basic regulation of food and water intake directly. It is known, however, that ACC plays an important role in feeding-related motivational processes [22], therefore, it can be assumed that, at least by evaluating the hedonic properties of the food, it takes part in the organization of the feeding behavior.

2. Body temperature, influence of paracetamol

Pyrogenic effect of IL-1β has long been known in the scientific literature [4-6, 8], our results are, however, the first to show that the cytokine microinjected into the ACC causes remarkable increase in body temperature. Based on the relevant literature, IL-1β stimulates the biotransformation of arachidonic acid and so it increases the prostaglandin E2 (PGE2) production of various cells [31, 32]. Fever is supposed to be developed by the action of PGE2 on the vascular organ of lamina terminalis and the anterior preoptic area (POA) [33-37]. It is important to note that POA is innervated by certain parts of the cortex, among others the cingulate cortex, and a considerable part of its neurons show responsiveness to the stimulation of this area [38].

In order to clarify the role of cyclooxygenase (COX) mediated processes in the background of the mechanism of action of IL-1β, paracetamol pretreatment was used in our experiments. Paracetamol exerts its effect by blocking the peroxidase activity of the COX-1 and COX-2 isoenzymes that leads to the inhibition of the biosynthesis of prostaglandins from arachidonic acid [39]. The pyrogenic effect of IL-1β by prostaglandins is mediated by COX-2 [40]. In our present study, paracetamol pretreatment into the ACC prohibited the significant body temperature increasing effect of IL-1β given into the same area, however, it did not prevent it completely. This means that although COX mediated processes obviously play an

important role in the development of fever induced by IL-1β, other mechanisms are supposed to be involved as well. It is known for example that the central adrenergic system takes part in the development of IL-1 induced fever [7], and it was also shown that certain cytokines – among others IL-1β – exert their body temperature increasing effect by the release of CRH, and this mechanism is not influenced by COX inhibitors [41, 42].

3. Metabolic role

Many articles have been published related to the effect of IL-1β on glucose homeostasis. Its hypoglycemia causing [10], and antidiabetic effect [11, 43] have been shown, other sources, however, state that it leads to the damage of insulin secretion [44-46], and suppose its contribution to the development of both type 1 and type 2 diabetes mellitus [47-51]. In our present study, no significant alterations in the blood glucose level of the animals were found in GTT, after IL-1β microinjection into the ACC.

Plasma level of lipoproteins decrease during the fever response in bacterial infections [52, 53], the level of triglycerides, however, is usually elevated during infections and inflammations [54, 55], and cytokines are supposed to play important mediating role in the processes leading to these alterations. In our present metabolic examinations, the significant decrease of the plasma concentrations of HDL and total cholesterol have been found. The level of triglycerides increased compared to the control animals, but this alteration did not reach the level of significance. Based on our present results and data from the relevant – somewhat contradictory – scientific literature, [8, 11, 12, 56] the existence of an IL-1β mediated central control mechanism that affects lipid metabolism is presumed. Actual alterations in the level of lipid metabolites are, however, the result of the interaction of several regulatory factors.

4. Taste reactivity

Our taste reactivity test results show that IL-1β bilaterally microinjected into the ACC cause taste reactivity alterations: lower concentration bitter and higher concentration umami taste solutions – that were “neutral” (no significant difference between the ingestive and aversive responses) for the control animals – were definitely pleasant for the IL-1β treated ones. In case of the higher concentration sweet taste solution – that proved to be delicious for the

control rats – the significant difference between the ingestive and aversive responses disappeared in the cytokine treated group.

Our results regarding the *umami* taste, are comparable to the findings of several human studies, where diseases associated with elevated levels of IL-1β were accompanied by the significant increase of the detection and recognition threshold of umami taste. Due to this shift, the patients felt this taste less intense and the number of hedonically positive responses increased [16, 17]. In our present experiment, lower concentration of the umami taste solution was clearly pleasant for the rats, which means that the above mentioned shift in the recognition threshold can give an explanation to these taste reactivity changes observed by us. The cited studies and our present results let us conclude that the increase of the recognition threshold for umami taste is presumably caused by the elevated concentration of IL-1β that affects the function of the ACC as well. Similar to the umami, altered detection threshold was described related to *bitter* taste as well in association with the elevation of IL-1β concentration [57], which can also explain the taste reactivity alteration found in case of this taste solution in our present series of experiments.

The shift in recognition threshold can not be the reason of the taste reactivity change seen in case of the higher concentration *sweet* solution, since the lower concentration of this taste proved to be obviously pleasant. It is known that cytokines have a substantial effect on energy balance by the maintained activation of the melanocortin system and inhibition of the neuropeptide Y pathway. This imbalance between the anorexigenic and orexigenic peptides causes the increase of saturation sensation [58, 59], which leads to the decrease of hedonic value of sweet taste both in human [60, 61], and in rodents [62, 63]. Alteration of taste reactivity reactions in response to the higher concentration sweet taste solution was not seen in case of the control group, in spite of the fact that the lower concentration sucrose was given as the third, and the higher concentration as the eighth taste stimulus in the tase reactivity test. All the above let us conclude that IL-1β caused saturation to develop earlier (at lower energy intake) than in the control group and consequently decreased the hedonic value of sweet taste.

It is important to highlight that from all tastes, sweet, bitter and umami – exactly those where we found taste reactivity changes – are the ones which determine the pleasantness and so the acceptance of a food the most [17]. That is, altered perception or hedonic value of these tastes has a huge impact on the food choice and appetite of a patient and so contributes to the difficulties of the maintenance of body weight and to the development of metabolic disorders.

5. Conditioned taste aversion

We examined the possible effect of IL-1β on feeding-related learning processes in conditioned taste aversion test. Our results show that the cytokine microinjected bilaterally into the ACC did not lead to the development of CTA, and it did not influence the LiCl-induced CTA either. Based on the relevant literature, IL-1β can elicit CTA under certain circumstances [64, 65], but – at least at the dose that was used in our experiment – it has no such functional role in cingulate cortical taste sensation associated learning processes.

6. Behavioral experiments: open field and conditioned place preference tests

Open field test was performed in order to examine the effect of IL-1β on the locomotor activity of the rats. Based on the related scientific literature, this effect of the cytokine is dose-dependent [66, 67]. Our present results show that IL-1β at the used dose did not decrease the activity of the animals, in fact, it increased their exploratory activity (rearing, locomotion). This means that our results found in the taste reactivity test are not only the consequences of the well-known effects (sicknss behavior, anxiety, decreased locomotion) of the cytokine.

Possible negative or positive reinforcing effect of IL-1β was examined in conditioned place preference test. Neither place aversion, nor place preference was seen at the used dose in our present experiment, which means that the cytokine did not evoke such positive or negative reinforcing effect that would influence the animals' taste sensation associated behavior. This further confirmed the results of the CTA test, where IL-1β microinjection did not lead to the development of conditioned taste aversion.

VI. Summary

1. IL-1β did not modify food and water intake of the animals significantly.
2. IL-1β caused significant elevation in the body temperature of the animals.

3. Paracetamol pretreatment was able to prevent this body temperature increase, that is, the role of prostaglandin-mediated processes in the mechanism of action of IL-1β has been proved.

4. There was no significant difference between the blood glucose levels of the IL-1β treated and control animals during GTT, though the dynamics of the two blood glucose curves obviously differed.

5. Significant decrease was shown in the plasma levels of HDL and total cholesterol due to the IL-1β treatment.

6. Alterations in the taste responsiveness of IL-1β treated rats were found in taste reactivity test in case of the following taste solutions: lower concentration quinine, higher concentration MSG and higher concentration sucrose.

7. IL-1β did not lead to the development of conditioned taste aversion.

8. LiCl-induced CTA was not influenced by the microinjection of the cytokine.

9. Exploratory activity (locomotion, rearing) of the animals was found to be increased by IL-1β in open field test.

10. Neither positive (place preference), nor negative (place aversion) reinforcing effect of IL-1β has been proved in place preference test.

VII. List of publications

cumulative impact factor: 26,987

I. Journal articles

A. Journal articles related to the thesis

Food and Water Intake, Body Temperature and Metabolic Consequences of interleukin-1β Microinjection Into the Cingulate Cortex of the Rat
B Csetényi, E Hormay, I Szabó, G Takács, B Nagy, K László, Z Karádi
Behav Brain Res. 2017 Jul 28;331:115-122.doi: 10.1016/j.bbr.2017.05.041. Epub 2017 May 17. **IF: 3,173**

Homeostatic significance of interleukin-1β in the cingulate cortex
Bettina Csetényi and Zoltán Karádi
Temperature (Austin). 2018; 5(2): 106–108. doi: 10.1080/23328940.2017.1420999. Published online 2018 Feb 15.

Disturbance of taste reactivity and other behavioral alterations after bilateral interleukin-1β microinjection into the cingulate cortex of the rat
László BR, Hormay E, Szabó I, Mintál K, Nagy B, László K, Péczely L, Ollmann T, Lénárd L, Karádi Z.
Behav Brain Res. 2020 Apr 6;383:112537. doi: 10.1016/j.bbr.2020.112537. Epub 2020 Feb 4. PMID: 32032742 **IF: 2,977**

B. Further journal articles

Noradrenaline and acetylcholine responsiveness of glucose-monitoring and glucose-insensitive neurons in the mediodorsal prefrontal cortex
Bernadett Nagy, István Szabó, Bettina Csetényi, Edina Hormay, Szilárd Papp, Dóra Keresztes, Zoltán Karádi
Brain Res. 2014 Jan 16;1543:159-64. doi: 10.1016/j.brainres.2013.11.014. Epub 2013 Nov 16. **IF: 2,843**

Impaired glucose tolerance after streptozotocin microinjection into the mediodorsal prefrontal cortex of the rat.
Nagy B, Szabó I, Takács G, Csetényi B, Hormay E, Karádi Z.
Physiol Int. 2016 Dec;103(4):403-412. doi: 10.1556/2060.103.2016.4.5. **IF: 0,571**

A medialis ventrolateralis praefrontalis (orbitofrontalis) kéreg glükózmonitorozó idegsejtjei szerepet játszanak a homeosztázis fenntartásában
Szabó I, Hormay E, Csetényi B, Nagy B, Karádi Z
Orv Hetil. 2017 May;158(18):692-700. doi: 10.1556/650.2017.30767. **IF: 0,322**

Multiple functional attributes of glucose-monitoring neurons in the medial orbitofrontal (ventrolateral prefrontal) cortex.
Szabo I, Hormay E, Csetenyi B, Nagy B, Lenard L, Karadi Z
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS 85: pp. 44-53. (2018) **IF: 8,002**

The role of intraamygdaloid neurotensin and dopamine interaction in conditioned place preference.
Laszlo K, Peczely L, Kovacs A, Zagoracz O, Ollmann T, Kertes E, Kallai V, Csetenyi B, Karadi Z, Lenard L
BEHAVIOURAL BRAIN RESEARCH 344: pp. 85-90. (2018) **IF: 2,77**

The effect of loss of the glucose-monitoring neurons in the anterior cingulate cortex: physiologic challenges induce complex feeding-metabolic alterations after local streptozotocin microinjection in rats.
Hormay, Edina; László, Bettina; Szabó, István; Ollmann, Tamás; Nagy, Bernadett; Péczely, László; Mintál, Kitti; Karádi, Zoltán
NEUROSCIENCE RESEARCH (2019) **IF: 2,645**

The role of D2 dopamine receptors in oxytocin induced place preference and anxiolytic effect.
Laszlo, K., Peczely, L., Geczi, F., Kovacs, A., Zagoracz, O., Ollmann, T., Kertes, E., Kallai, V., Laszlo, B., Berta, B., Karadi, Z., Lenard, L.
Horm Behav, 2020. 124: p. 104777. **IF: 3,684**

II. Further publications

Az idegsejtek komplex funkcionális sajátosságai az orbitofrontalis kéregben
Dr. Szabó István, Dr. Nagy Bernadett, Cseténvi Bettina, Hormay Edina, Bajnok Góré Márk, Prof. Dr. Karádi Zoltán
II. INTERDISZCIPLINÁRIS DOKTORANDUSZ KONFERENCIA 2013, Konferenciakötet, 435. oldal, ISBN 978-963-642-598-2

Cinguláris kérgi IL-1β mikroinjekció hatása a táplálkozásra és anyagcserére laboratóriumi patkányban
Cseténvi Bettina, Hormay Edina, Nagy Bernadett, Szabó István, Bajnok Góré Márk, Hideg Barnabás és Karádi Zoltán
III. Interdiszciplináris Doktorandusz Konferencia 2014. Konferenciakötet ISBN 978-963-642-741-2 Pécs, 2015.

A cinguláris kéreg streptozotocin mikroinjekciójának hatása a glukóz toleranciára laboratóriumi patkányban
Hormay Edina, Cseténvi Bettina, Szabó István, Nagy Bernadett, Hideg Barnabás, Bajnok Góré Márk és Karádi Zoltán
III. Interdiszciplináris Doktorandusz Konferencia 2014. Konferenciakötet ISBN 978-963-642-741-2 Pécs, 2015.

A cinguláris kérgi glukóz monitorozó neuronok szerepe a táplálkozás és anyagcsere szabályozásban
Hormay E, Cseténvi B, Szabó I, Nagy B, Torda V, Tóth M, Karádi Z
OBESITOLOGIA HUNGARICA 16:(Suppl1) p. 14. (2017)

Íz-érzékelés a gasztrointesztinális rendszerben
Szabó I, Hormay E, Cseténvi B, Karádi Z.
Tavaszi Szél 2018 – Tanulmánykötet (2018)

Endogenous and exogenous chemical responsiveness in nucleus accumbens
Szabó I, Hormay E, Cseténvi B, Karádi Z.
VII. Interdiszciplináris Doktorandusz Konferencia – Tanulmánykötet (2018)

III. Conference attendances

A. Lectures

Interleukin-1β microinjection into the cingulate cortex induces homeostatic changes in the rat
Bettina Cseténvi, Edina Hormay, Bernadett Nagy, István Szabó, Márk Bajnok Góré, Barnabás Hideg, and Zoltán Karádi
2nd International Doctoral Workshop on Natural Sciences 2013 Pécs

Az idegsejtek komplex funkcionális sajátosságai az orbitofrontalis kéregben
Szabó, I., Nagy, B., Cseténvi, B., Hormay, E., Bajnok Góré, M., Karádi, Z.
IDK 2013 Pécs

Complex functional attributes of neurons in the cingulate cortex of the rat
Hormay, E., Cseténvi, B., Szabó, I., Nagy, B., Bajnok Góré, M., Karádi Z.
2nd International Doctoral Workshop on Natural Sciences 2013 Pécs

Metabolic alterations after streptozotocin microinjection into the mediodorsal prefrontal cortex
Nagy, B., Szabó, I., Cseténvi, B., Hormay, E., Bajnok Góré, M., Karádi Z.
2nd International Doctoral Workshop on Natural Sciences 2013 Pécs

IL-1β mikroinjekció homeosztatikus hatásai patkány cinguláris kérgében
Cseténvi Bettina, Hormay Edina, Nagy Bernadett, Szabó István, Bajnok Góré Márk, Hideg Barnabás, Karádi Zoltán
A Pécsi Tudományegyetem Idegtudományi Centrum (PTE IC) Tudományos Diákköri és Doktorandusz Konferenciája, 2014 Pécs

Patkány cinguláris kérgébe adott IL-1β mikroinjekció homeosztatikus hatásainak vizsgálata
Csetényi Bettina, Hormay Edina, Nagy Bernadett, Szabó István, Karádi Zoltán
Tavaszi Szél Konferencia 2015, Eger Absztraktkötet: ISBN: 978-963-397-702-6

Cinguláris kérgi IL-1β mikroinjekció homeosztatikus hatásainak vizsgálata patkányban
Csetényi Bettina, Hormay Edina, Nagy Bernadett, Szabó István, Tóth Mátyás, Torda Viktor, Karádi Zoltán
Doctoral Workshop 2015, Pécs

Glukóz tolerancia változások laboratóriumi patkányban cinguláris kérgi streptozotocin mikroinjekciót követően
Hormay Edina, Csetényi Bettina, Szabó István, Nagy Bernadett, Karádi Zoltán
Tavaszi Szél Konferencia 2015, Eger Absztraktkötet: ISBN: 978-963-397-702-6

A medialis orbitofrontalis kérgi glukóz-monitorozó idegsejtek komplex funkcionális sajátosságai
Szabó István, Hormay Edina, Csetényi Bettina, Nagy Bernadett, Karádi Zoltán
Tavaszi Szél Konferencia 2015, Eger Absztraktkötet: ISBN: 978-963-397-702-6

Effect of stress associated neurotransmitters on the mediodorsal prefrontal cortex
B Nagy, I Szabó, B Csetényi, E Hormay, Z Karádi
5th International Regional (North America) ISBS Neuroscience and Biological Psychiatry „Stress and Behavior" Conference, Miami, FL, USA, 2015

Complex functional atributes of orbitofrontal cortical glucose-monitoring neurons
István Szabó, Edina Hormay, Bettina Csetényi, Viktor Torda, Mátyás Tóth, Zoltán Karádi
CECON 2015, Budapest OBESITOLOGIA HUNGARICA 14:(Suppl2) p. 58. (2015)

A medialis orbitofrontalis kérgi glukóz-monitorozó idegsejtek metabolikus és magatartási funkcióinak vizsgálata patkányban
Szabó István, Hormay Edina, Csetényi Bettina, Torda Viktor, Tóth Mátyás, Karádi Zoltán
Doctoral Workshop 2015, Pécs

Patkány cinguláris kérgi glukóz-monitorozó neuronok táplálkozási és metabolikus szerepe
Hormay Edina, Csetényi Bettina, Nagy Bernadett, Szabó István, Torda Viktor, Tóth Mátyás és Karádi Zoltán
Doctoral Workshop 2015, Pécs

Glucose-monitoring neurons in the medial orbitofrontal cortex of rat
Istvan Szabo, Edina Hormay, Bettina Csetenyi, Zoltan Karadi
IBNS 2016 Annual Meeting, Budapest, 2016

A mediális orbitofrontális kérgi glukóz-monitorozó idegsejtek metabolikus szerepe a homeosztázis szabályozásában
Szabó István, Hormay Edina, Cseténvi Bettina, Karádi Zoltán
Tavaszi Szél Konferencia, Miskolc, 2017

A cinguláris kérgi glukóz monitorozó neuronok szerepe a táplálkozás és anyagcsere szabályozásban
Hormay Edina, Cseténvi Bettina, Szabó István, Karádi Zoltán
A Magyar Elhízástudományi Társaság 25. éves Jubileumi Kongresszusa, Budapest, 2017
OBESITOLOGIA HUNGARICA 16:(Suppl1) p. 14. ISSN 1586-7935 (2017)

Az interleukin-1β ízpercepciót módosító hatása patkány cinguláris kérgében
CSETÉNYI Bettina Réka, Hormay Edina, Szabó István, Mintál Kitti, Karádi Zoltán
Tavaszi Szél Konferencia, 2018, Győr

Ízérzékelés a gasztrointesztinális rendszerben?
Szabó István, Hormay Edina, Cseténvi Bettina, Karádi Zoltán
Tavaszi Szél Konferencia 2018, Győr, 2018

Taste responsiveness of neurons in nucleus accumbens
Szabó István, Hormay Edina, Cseténvi Bettina, Karádi Zoltán
VII. Interdiszciplináris Doktorandusz Konferencia, Pécs, 2018

A nucleus accumbens ízérzékelésben betöltött szerepének vizsgálata elektrofiziológiai módszerekkel szabadon mozgó patkányokban
Szabó István, Hormay Edina, László Bettina, Karádi Zoltán
XXII. Tavaszi Szél Konferencia, Debrecen, 2019

Limbikus előagyi neuronok szerepe a táplálkozás és az anyagcsere szabályozásában
Szabó István, Hormay Edina, László Bettina, Lénárd László, Karádi Zoltán
FAMÉ 2019, Budapest

B. Poster presentations

Endogén és exogén kémiai ingerek hatása az umami-érzékeny idegsejtekre patkány cinguláris kérgében
Cseténvi Bettina, Hormay Edina, Szabó István, Nagy Bernadett, Hideg Barnabás, Faragó Bence, Bajnok Góré Márk, Karádi Zoltán
MÉT 2012 Debrecen

Patkány cinguláris kéreg glukóz-monitorozó idegsejtjeinek exogén és endogén kémiai érzékenysége
Hormay Edina, Cseténvi Bettina, Szabó István, Nagy Bernadett, Faragó Bence, Hideg Barnabás, Bajnok Góré Márk és Karádi Zoltán
MÉT 2012 Debrecen

Homeostatic alterations after IL-1β microinjection into the cingulate cortex of the rat
Bettina Csetényi, Edina Hormay, Bernadett Nagy, István Szabó, Márk Bajnok Góré, Barnabás Hideg, and Zoltán Karádi
MITT 2013 Budapest

A cinguláris kéregbe adott IL-1β mikroinjekció homeosztatikus hatásai patkányban
Cseténi Bettina, Hormay Edina, Nagy Bernadett, Szabó István, Bajnok Góré Márk, Hideg Barnabás, Karádi Zoltán
MÉT 2013 Budapest

Catecholamine responsiveness of glucose-monitoring neurons in the cingulate cortex of the rat
Edina Hormay, Bettina Cseténi, István Szabó, Bernadett Nagy, Barnabás Hideg, Márk Bajnok Góré and Zoltán Karádi
MITT 2013 Budapest

Endogenous and exogenous chemical responsiveness in the medial orbitofrontal cortex
Szabó, I., Nagy, B., Cseténi, B., Hormay, E., Bajnok Góré, M., Karádi, Z.
MITT 2013 Budapest

A glukóz-monitorozó idegsejtek katekolamin érzékenysége és intraorális íz-ingerlésre adott válaszai patkány cinguláris kérgében
Hormay Edina, Cseténi Bettina, Szabó István, Nagy Bernadett, Hideg Barnabás, Bajnok Góré Márk, Karádi Zoltán
MÉT 2013 Budapest

Kóros glukóz tolerancia a mediodorzális prefrontális kéreg streptozotocin mikroinjekcióját követően patkányban
Nagy Bernadett, Szabó István, Cseténi Bettina, Hormay Edina, Bajnok Góré Márk, Karádi Zoltán
MÉT 2013 Budapest

Medialis és lateralis orbitofrontalis kérgi idegsejtek komplex funkcionális sajátosságai
Szabó, I., Nagy, B., Cseténi, B., Hormay, E., Bajnok Góré, M., Karádi, Z.
MÉT 2013 Budapest

Neurochemical responsiveness and taste sensitivity of neurons in the medial and lateral orbitofrontal cortex of the rat
Szabó, I., Nagy, B., Cseténi, B., Hormay, E., Bajnok Góré, M., Karádi Z.
2nd International Doctoral Workshop on Natural Sciences 2013 Pécs

Feeding and metabolic consequences of IL-1β microinjection into the cingulate cortex in the rat
Bettina Cseténi, Edina Hormay, Bernadett Nagy, István Szabó, Márk Bajnok Góré, Barnabás Hideg, and Zoltán Karádi
IBRO 2014 Debrecen

Cinguláris kérgi IL-1β mikroinjekció hatásai a táplálkozásra és anyagcserére laboratóriumi patkányban
Cseténvi Bettina, Hormay Edina, Nagy Bernadett, Szabó István, Bajnok Góré Márk, Hideg Barnabás, Karádi Zoltán
IDK 2014 Pécs

IL-1β modifies the taste reactivity in the cingulate cortex of the rat
Bettina Cseténvi, Edina Hormay, Bernadett Nagy, István Szabó, Márk Bajnok Góré, and Zoltán Karádi
FEPS-MÉT 2014 Budapest ACTA PHYSIOLOGICA 211:(697) pp. 143-144. (2014)

Streptozotocin microinjection into the cingulate cortex alters glucose tolerance in the rat
Edina Hormay, Bettina Cseténvi, István Szabó, Bernadett Nagy, Barnabás Hideg, Márk Bajnok Góré and Zoltán Karádi
IBRO 2014 Debrecen

Metabolic Effects of Local Microinjection of Streptozotocin into the Mediodorsal Prefrontal Cortex
Bernadett Nagy, István Szabó, Bettina Cseténvi, Edina Hormay, Márk Bajnok Góré and Zoltán Karádi
IBRO 2014 Debrecen

Nucleus Accumbens and Orbitofrontal Cortex: Endogenous and Exogenous Chemical Responsiveness of Neurons in the Rat
István Szabó, Bernadett Nagy, Edina Hormay, Bettina Cseténvi, Márk Bajnok Góré, Zoltán Karádi
IBRO 2014 Debrecen

A cinguláris kéreg streptozotocin mikroinjekciójának hatása a glukóz toleranciára laboratóriumi patkányban
Hormay Edina, Cseténvi Bettina, Szabó István, Nagy Bernadett, Hideg Barnabás, Bajnok Góré Márk és Karádi Zoltán
IDK 2014 Pécs

Complex functional attributes of glucose-monitoring neurons in medial orbitofrontal cortex and their homeostatic significance
István Szabó, E. Hormay, B. Cseténvi, B. Nagy, M. Bajnok Góré, Z. Karádi
FEPS-MÉT 2014, Budapest ACTA PHYSIOLOGICA 211:(697) p. 150. (2014)

Complex functional attributes of cingulate cortex glucose-monitoring neurons and their metabolic significance
Edina Hormay, B. Cseténvi, I. Szabó, B. Nagy, B. Hideg, M.B. Góré, Z. Karádi
FEPS-MÉT 2014, Budapest ACTA PHYSIOLOGICA 211:(697) p. 144. (2014)

Cingulate cortex IL-1β mediated mechanisms in the regulation of feeding and metabolism in the rat
B Csetényi, E Hormay, B Nagy, I Szabó, M Tóth, V Torda, Z Karádi
CECON 2015, Budapest OBESITOLOGIA HUNGARICA 14:(Suppl2) pp. 57-58. (2015)

A cinguláris kéreg streptozotocin mikroinjekciójának metabolikus hatása laboratóriumi patkányban
Hormay Edina, Cseténvi Bettina, Nagy Bernadett, Szabó István, Karádi Zoltán
A MÉT 79. Vándorgyűlése és a MMVBT 2015. évi Konferenciája, Szeged

A medialis orbitofrontalis kéregbe adott streptozotocin mikroinjekció metabolikus és magatartási hatásai patkányban
Szabó István, Hormay Edina, Cseténvi Bettina, Nagy Bernadett, Karádi Zoltán
A MÉT 79. Vándorgyűlése és a MMVBT 2015. évi Konferenciája, Szeged

Medial Orbitofrontal Cortex: Complex Functional Attributes of Glucose-Monitoring Neurons and Their Metabolic Significance
I Szabó, E Hormay, B Cseténvi, B Nagy, M Bajnok Góré, Z Karádi
MITT; Budapest, 2015

Glucose-monitoring neurons of the rat cingulate cortex: feeding and metabolic significance
E Hormay, B Cseténvi, I Szabó, B Nagy, V Torda, M Tóth, Z Karádi
CECON 2015, Budapest OBESITOLOGIA HUNGARICA 14:(Suppl2) pp. 57. (2015)

Cinguláris kérgi interleukin-1β mikroinjekció íz-percepciót módosító hatásának vizsgálata patkányban
Cseténvi Bettina, Hormay Edina, Szabó István, Nagy Bernadett, Karádi Zoltán
FAMÉ 2016, Pécs

Patkány cinguláris kérgi glukóz-monitorozó neuronok elektrofiziológiai sajátosságai és metabolikus jelentősége
Hormay Edina, Cseténvi Bettina, Szabó István, Karádi Zoltán
FAMÉ 2016 Pécs

A glukóz-monitorozó neuronok komplex funkcionális sajátosságai a medialis orbitofrontalis kéregben
Szabó István, Hormay Edina, Cseténvi Bettina, Nagy Bernadett, Karádi Zoltán
FAMÉ 2016, Pécs

Cinguláris kérgi interleukin-1β mikroinjekció metabolikus hatásai patkányban
Cseténvi Bettina, Hormay Edina, Szabó István, Karádi Zoltán
ÉFM (MÉT) 2017, Debrecen

Metabolic effects of interleukin-1β microinjection into the cingulate cortex of the rat
Cseténvi B, Hormay E, Szabó I, Karádi Z
FENS; Pécs, 2017

Metabolic alterations after interleukin-1β microinjection into the cingulate cortex of the rat
Bettina Csetényi, Edina Hormay, István Szabó, Zoltán Karádi
CECON; Pozsony, 2017

A medialis orbitofrontalis kérgi glukóz-monitorozó neuronok szerepe a homeosztázis fenntartásában
Szabó István, Hormay Edina, Csetényi Bettina, Karádi Zoltán
ÉFM (MÉT); Debrecen, 2017

Multiple functional significance of the glucose-monitoring neuronal network in the medial orbitofrontal cortex
Istvan Szabo, Edina Hormay, Bettina Csetenyi, Zoltan Karadi
IBNS; Hiroshima, 2017

Feeding and metabolic attributes of the glucose monitoring-neurons in the cingulate cortex
Edina Hormay, Bettina Csetényi, István Szabó, Zoltán Karádi
FENS; Pécs, 2017

The role of medial orbitofrontal cortical glucose-monitoring neurons in the maintenance of homeostasis
István Szabó, Edina Hormay, Bettina Csetényi, Zoltán Karádi
FENS, Pécs, 2017

Feeding and metabolism altering attributes of the glucose-monitoring neurons in the cingulate cortex of the rat
Edina Hormay, Bettina Csetényi, István Szabó, Zoltán Karádi
CECON; Pozsony, 2017

Íz-reaktivitás változások patkány cinguláris kérgébe adott interleukin-1β hatására
Csetényi Bettina, Hormay Edina, Szabó István, Mintál Kitti, Karádi Zoltán
MÉT, Szeged, 2018

The role of intraamygdaloid oxytocin in novel object recognition memory
László K., Ollmann T., Kovács A., Zagoracz O., Péczely L., Kertes E., Csetényi B., Karádi Z., Lénárd L.
Magyar Élettani Társaság Vándorgyűlése, Szeged, 2018

Az idegsejtek komplex funkcionális sajátosságai a nucleus accumbens-ben
Szabó István, Hormay Edina, Csetényi Bettina, Karádi Zoltán
Magyar Élettani Társaság Vándorgyűlése, Szeged, 2018

Endogenous and exogenous chemical responsiveness in nucleus accumbens
Szabó István, Hormay Edina, Csetényi Bettina, Karádi Zoltán
VII. Interdiszciplináris Doktorandusz Konferencia (IDK), Pécs, 2018

New methodological approach for the examination of taste and texture detection of neurons
Szabó István, Hormay Edina, László Bettina, Karádi Zoltán
Medical Conference for PhD Students and Experts of Clinical Sciences 2018 (MEDPécs), Pécs, 2018

Taste reactivity alterations after interleukin-1β microinjection into the cingulate cortex of the rat
Bettina Réka László, Edina Hormay, István Szabó, Kitti Mintál, Zoltán Karádi
MITT, Debrecen, 2019

Glucose-monitoring neurons in the cingulate cortex of the rat. – Microelectrophysiological study
Edina Hormay, Bettina László, István Szabó, Kitti Mintál, Zoltán Karádi
16th Annual Conference of the Hungarian Neuroscience Society (MITT), Debrecen, 2019

Inhibition of dopamine D2 receptors can alter the positive reinforcing and anxiolytic effects of oxytocin
K László, T Ollmann, O Zagoracz, L Péczely, E Kertes, A Kovács, V Kállai, BR László, B Berta, Z Karádi, L Lénárd
16th Annual Conference of the Hungarian Neuroscience Society (MITT), Debrecen, 2019

Electrophysiological examination of underlying neuronal mechanisms of taste reactivity in the nucleus accumbens of behaving rats
Istvan Szabo, Edina Hormay, Bettina Laszlo, Zoltan Karadi
16th Annual Conference of the Hungarian Neuroscience Society (MITT), Debrecen, 2019

Electrophysiological examination of neurons during taste reactivity test in the nucleus accumbens and medial orbitofrontal cortex of the rat
Istvan Szabo, Edina Hormay, Bettina Laszlo, Zoltan Karadi
13th Göttingen Meeting of the German Neuroscience Society, Göttingen, Németország, 2019

Examination of the role of neurons in taste reactivity
István Szabó, Edina Hormay, Bettina László, Zoltán Karádi
Interdisciplinary Doctoral Conference (IDK) 2019, Pécs

Behavioral alterations after bilateral microinjection of interleukin-1β into the cingulate cortex of the rat
Bettina Réka László, Edina Hormay, István Szabó, Kitti Mintál, Kristóf László, László Péczely, Tamás Ollmann, László Lénárd and Zoltán Karádi
IBRO, Szeged, 2020

Intraamygdaloid oxytocin reduces anxiety in valproate-induced autism model
László Kristóf, Géczi Fanni, Ollmann Tamás, Kovács Anita, Péczely László, László Bettina, Kállai Veronika, Kertes Erika, Berta Beáta, Karádi Zoltán, Lénárd László
IBRO, Szeged, 2020

VIII. References

1. Kent, S., et al., *Reduction in food and water intake induced by microinjection of interleukin-1 beta in the ventromedial hypothalamus of the rat.* Physiol Behav, 1994. **56**(5): p. 1031-1036.
2. Langhans, W., D. Savoldelli, and S. Weingarten, *Comparison of the feeding responses to bacterial lipopolysaccharide and interleukin-1 beta.* Physiol Behav, 1993. **53**(4): p. 643-9.
3. Plata-Salaman, C.R., Y. Oomura, and Y. Kai, *Tumor necrosis factor and interleukin-1 beta: suppression of food intake by direct action in the central nervous system.* Brain Res, 1988. **448**(1): p. 106-14.
4. Karadi, Z., et al., *Homeostatic alterations after intrapallidal microinjection of interleukin-1beta in the rat.* Appetite, 2005. **44**(2): p. 171-80.
5. Dascombe, M.J., et al., *Pyrogenic and thermogenic effects of interleukin 1 beta in the rat.* Am J Physiol, 1989. **256**(1 Pt 1): p. E7-11.
6. Lukats, B., et al., *Homeostatic alterations induced by interleukin-1beta microinjection into the orbitofrontal cortex in the rat.* Appetite, 2005. **45**(2): p. 137-47.
7. Ovadia, H., O. Abramsky, and J. Weidenfeld, *Evidence for the involvement of the central adrenergic system in the febrile response induced by interleukin-1 in rats.* J Neuroimmunol, 1989. **25**(2-3): p. 109-16.
8. Takacs, G., et al., *Homeostatic alterations after IL-1beta microinjection into the nucleus accumbens of the rat.* Appetite, 2010. **54**(2): p. 354-362.
9. Bendtzen, K., et al., *Cytotoxicity of human pI 7 interleukin-1 for pancreatic islets of Langerhans.* Science, 1986. **232**(4757): p. 1545-7.
10. del Rey, A. and H. Besedovsky, *Interleukin 1 affects glucose homeostasis.* Am J Physiol, 1987. **253**(5 Pt 2): p. R794-8.
11. del Rey, A., et al., *Metabolic and endocrine effects of interleukin-1 in obese, diabetic Zucker fa/fa rats.* Exp Clin Endocrinol Diabetes, 1996. **104**(4): p. 317-26.
12. Hermus, A.R., et al., *Continuous infusion of interleukin-1 beta in rats induces a profound fall in plasma levels of cholesterol and triglycerides.* Arterioscler Thromb, 1992. **12**(9): p. 1036-43.
13. Aubert, A. and R. Dantzer, *The taste of sickness: lipopolysaccharide-induced finickiness in rats.* Physiol Behav, 2005. **84**(3): p. 437-44.
14. Cohn, Z.J., et al., *Lipopolysaccharide-induced inflammation attenuates taste progenitor cell proliferation and shortens the life span of taste bud cells.* BMC Neurosci, 2010. **11**: p. 72.
15. Larson, S.J., *Lipopolysaccharide and interleukin-1beta decrease sucrose intake but do not affect expression of place preference in rats.* Pharmacol Biochem Behav, 2006. **84**(3): p. 429-35.
16. Musialik, J., et al., *Taste and appetite disorders in patients with non-alcoholic fatty liver disease.* Journal of Hepatology, 2017. **66**(1): p. S417-S417.
17. Musialik, J., et al., *Taste and appetite disorders of chronic hepatitis C patients.* European Journal of Gastroenterology & Hepatology, 2012. **24**(12): p. 1400-1405.
18. Schalk, P., et al., *Influence of cancer and acute inflammatory disease on taste perception: a clinical pilot study.* Support Care Cancer, 2018. **26**(3): p. 843-851.
19. Tataranni, P.A., et al., *Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography.* Proc Natl Acad Sci U S A, 1999. **96**(8): p. 4569-74.
20. Farrell, M.J., et al., *Effect of aging on regional cerebral blood flow responses associated with osmotic thirst and its satiation by water drinking: a PET study.* Proc Natl Acad Sci U S A, 2008. **105**(1): p. 382-7.
21. Bie-Olsen, L.G., et al., *Changes of Cognition and Regional Cerebral Activity During Acute Hypoglycemia in Normal Subjects: A H-2 O-15 Positron Emission Tomographic Study.* Journal of Neuroscience Research, 2009. **87**(8): p. 1922-1928.
22. Martin, L.E., et al., *Neural mechanisms associated with food motivation in obese and healthy weight adults.* Obesity (Silver Spring), 2010. **18**(2): p. 254-60.

23. Stoeckel, L.E., et al., *Widespread reward-system activation in obese women in response to pictures of high-calorie foods.* Neuroimage, 2008. **41**(2): p. 636-47.
24. Grabenhorst, F., et al., *How the brain represents the reward value of fat in the mouth.* Cereb Cortex, 2010. **20**(5): p. 1082-91.
25. Rolls, E.T., *Functions of the orbitofrontal and pregenual cingulate cortex in taste, olfaction, appetite and emotion.* Acta Physiol Hung, 2008. **95**(2): p. 131-64.
26. Rolls, E.T., *Taste, olfactory and food texture reward processing in the brain and the control of appetite.* Proc Nutr Soc, 2012. **71**(4): p. 488-501.
27. Grill, H.J. and R. Norgren, *Taste Reactivity Test .1. Mimetic Responses to Gustatory Stimuli in Neurologically Normal Rats.* Brain Research, 1978. **143**(2): p. 263-279.
28. Tzschentke, T.M., *Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues.* Prog Neurobiol, 1998. **56**(6): p. 613-72.
29. Hasenohrl, R.U., M.S. Oitzl, and J.P. Huston, *Conditioned Place Preference in the Corral - a Procedure for Measuring Reinforcing Properties of Drugs.* Journal of Neuroscience Methods, 1989. **30**(2): p. 141-146.
30. Laszlo, K., et al., *Positive reinforcing effect of oxytocin microinjection in the rat central nucleus of amygdala.* Behav Brain Res, 2016. **296**: p. 279-285.
31. Kunkel, S.L., S.W. Chensue, and S.H. Phan, *Prostaglandins as endogenous mediators of interleukin 1 production.* J Immunol, 1986. **136**(1): p. 186-92.
32. Newton, R.C. and M. Covington, *The activation of human fibroblast prostaglandin E production by interleukin 1.* Cell Immunol, 1987. **110**(2): p. 338-49.
33. Boulant, J.A., *Role of the preoptic-anterior hypothalamus in thermoregulation and fever.* Clin Infect Dis, 2000. **31 Suppl 5**: p. S157-61.
34. Matsuda, T., T. Hori, and T. Nakashima, *Thermal and PGE2 sensitivity of the organum vasculosum lamina terminalis region and preoptic area in rat brain slices.* J Physiol, 1992. **454**: p. 197-212.
35. Stitt, J.T., *Prostaglandin E as the neural mediator of the febrile response.* Yale J Biol Med, 1986. **59**(2): p. 137-49.
36. Stitt, J.T., *Evidence for the involvement of the organum vasculosum laminae terminalis in the febrile response of rabbits and rats.* J Physiol, 1985. **368**: p. 501-11.
37. Evans, S.S., E.A. Repasky, and D.T. Fisher, *Fever and the thermal regulation of immunity: the immune system feels the heat.* Nat Rev Immunol, 2015. **15**(6): p. 335-49.
38. Kazakov, V.N., et al., *Influences from different areas of the cerebral cortex on preoptic neurons: morphological and electrophysiological data.* Neuroscience, 1992. **51**(4): p. 961-72.
39. Graham, G.G., et al., *The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings.* Inflammopharmacology, 2013. **21**(3): p. 201-32.
40. Li, S., et al., *Cyclooxygenase-2 mediates the febrile response of mice to interleukin-1beta.* Brain Res, 2001. **910**(1-2): p. 163-73.
41. Rothwell, N.J. and S.J. Hopkins, *Cytokines and the Nervous-System .2. Actions and Mechanisms of Action.* Trends in Neurosciences, 1995. **18**(3): p. 130-136.
42. Rothwell, N.J., *CRF is involved in the pyrogenic and thermogenic effects of interleukin 1 beta in the rat.* Am J Physiol, 1989. **256**(1 Pt 1): p. E111-5.
43. del Rey, A. and H. Besedovsky, *Antidiabetic effects of interleukin 1.* Proc Natl Acad Sci U S A, 1989. **86**(15): p. 5943-7.
44. Eizirik, D.L. and T. Mandrup-Poulsen, *A choice of death--the signal-transduction of immune-mediated beta-cell apoptosis.* Diabetologia, 2001. **44**(12): p. 2115-33.
45. Donath, M.Y. and T. Mandrup-Poulsen, *The use of interleukin-1-receptor antagonists in the treatment of diabetes mellitus.* Nat Clin Pract Endocrinol Metab, 2008. **4**(5): p. 240-1.
46. Dinarello, C.A., M.Y. Donath, and T. Mandrup-Poulsen, *Role of IL-1beta in type 2 diabetes.* Curr Opin Endocrinol Diabetes Obes, 2010. **17**(4): p. 314-21.
47. Rabinovitch, A., *An update on cytokines in the pathogenesis of insulin-dependent diabetes mellitus.* Diabetes Metab Rev, 1998. **14**(2): p. 129-51.

48. Banerjee, M. and M. Saxena, *Interleukin-1 (IL-1) family of cytokines: role in type 2 diabetes.* Clin Chim Acta, 2012. **413**(15-16): p. 1163-70.
49. Feve, B. and J.P. Bastard, *The role of interleukins in insulin resistance and type 2 diabetes mellitus.* Nat Rev Endocrinol, 2009. **5**(6): p. 305-11.
50. Guest, C.B., et al., *The implication of proinflammatory cytokines in type 2 diabetes.* Front Biosci, 2008. **13**: p. 5187-94.
51. Maedler, K., et al., *Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets.* J Clin Invest, 2002. **110**(6): p. 851-60.
52. Alvarez, C. and A. Ramos, *Lipids, lipoproteins, and apoproteins in serum during infection.* Clin Chem, 1986. **32**(1 Pt 1): p. 142-5.
53. Sammalkorpi, K., et al., *Changes in serum lipoprotein pattern induced by acute infections.* Metabolism, 1988. **37**(9): p. 859-65.
54. Kaufmann, R.L., et al., *Defective lipid disposal mechanisms during bacterial infection in rhesus monkeys.* Metabolism, 1976. **25**(6): p. 615-24.
55. Rouzer, C.A. and A. Cerami, *Hypertriglyceridemia associated with Trypanosoma brucei brucei infection in rabbits: role of defective triglyceride removal.* Mol Biochem Parasitol, 1980. **2**(1): p. 31-8.
56. Feingold, K.R., et al., *Effect of interleukin-1 on lipid metabolism in the rat. Similarities to and differences from tumor necrosis factor.* Arterioscler Thromb, 1991. **11**(3): p. 495-500.
57. Richardson, R.A. and H.I. Davidson, *Nutritional demands in acute and chronic illness.* Proc Nutr Soc, 2003. **62**(4): p. 777-81.
58. Inui, A., *Cancer anorexia-cachexia syndrome: are neuropeptides the key?* Cancer Res, 1999. **59**(18): p. 4493-501.
59. Perboni, S. and A. Inui, *Anorexia in cancer: role of feeding-regulatory peptides.* Philos Trans R Soc Lond B Biol Sci, 2006. **361**(1471): p. 1281-9.
60. Cabanac, M., *Physiological role of pleasure.* Science, 1971. **173**(4002): p. 1103-7.
61. Cabanac, M., *Sensory pleasure.* Q Rev Biol, 1979. **54**(1): p. 1-29.
62. Berridge, K.C., *Modulation of taste affect by hunger, caloric satiety, and sensory-specific satiety in the rat.* Appetite, 1991. **16**(2): p. 103-20.
63. Cabanac, M. and L. Lafrance, *Postingestive alliesthesia: the rat tells the same story.* Physiol Behav, 1990. **47**(3): p. 539-43.
64. Janz, L.J., et al., *Conditioned taste aversion but not adrenal activity develops to ICV administration of interleukin-1 in rats.* Physiol Behav, 1991. **49**(4): p. 691-4.
65. Tazi, A., et al., *Interleukin-1 induces conditioned taste aversion in rats: a possible explanation for its pituitary-adrenal stimulating activity.* Brain Res, 1988. **473**(2): p. 369-71.
66. Swiergiel, A.H. and A.J. Dunn, *Effects of interleukin-1beta and lipopolysaccharide on behavior of mice in the elevated plus-maze and open field tests.* Pharmacol Biochem Behav, 2007. **86**(4): p. 651-9.
67. Montkowski, A., et al., *Central administration of IL-1 reduces anxiety and induces sickness behaviour in rats.* Pharmacol Biochem Behav, 1997. **58**(2): p. 329-36.