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LIMBIC FOREBRAIN INTERLEUKIN-1β MECHANISMS IN THE CENTRAL REGULATION OF FEEDING, TASTE PERCEPTION AND METABOLISM

Ph.D. Thesis

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I. Introduction

The adaptation to the continuously changing environmental conditions, the assurance of certain biological functions, in other words, the maintenance of homeostasis is essentially important for the survival of the living organisms. During the support of the balance of the internal environment our organism provides the appropriate food and fluid intake, heat regulation and the level of different metabolites by complex, coordinated control mechanisms. In these processes, the immunoregulators, which exert multiple biological activities on several types of cells, have a pivotal role. The increased synthesis, secretion and utilization of numerous mediator molecules, particularly the cytokines, can be observed during these reactions. The *interleukin-1 (IL-1)* group is one of the most important representatives of the cytokines. IL-1 is present in two isoforms (α and β) and the latter seems to be biologically more important both in rodents and primates.

The synthesis of IL-1β were described both peripherally and in the central nervous system (CNS). It is produced peripherally by monocytes, macrophages, lymphocytes, fibroblasts and endothelial cells [12,13]. It has already been reported that centrally, macrophages intrinsic to the brain [28], cerebrovascular endothelial cells [4], microglia [19], astrocytes [17] and even neurons can synthesize and release IL-1 [6]. IL-1β-like immunoreactive fibers were shown in different areas of the brain, such as the nuclei of the hypothalamus (HT), the amygdala (AMY), nucleus tractus solitarii, locus coeruleus, etc., and the mRNA of IL-1β was detected among others in the *nucleus accumbens (NAcc)* and the *ventromedial hypothalamus (VMH)* [6,7]. The pyrogenic effect of the acutely and chronically applied primary cytokine was described both centrally and peripherally in numerous experiments, in which prostaglandin mechanisms were proven to be involved [51]. It was also verified that IL-1β induces slow wave sleep that leads to somnolence [65]. With regard to this it is worth mentioning that in infections or in long-lasting chronic illnesses decreased locomotory, exploratory activity and somnolence can be observed in humans. The role of IL-1β in the central regulation of feeding and metabolism seems to be particularly important. The primary cytokine exerts its anorexigenic effect through direct CNS mechanism, the intracerebroventricular (i.c.v.) injection of its low dose decreases significantly the food intake of rodents [53]. These observations show that IL-1β has the same or even more pronounced effect after direct cerebral than after peripheral administration. It seems that these cytokine mediated multiple central mechanisms are intimately involved in the homeostatic regulatory functions.

Beyond the results of the behavioral investigations we already have data about the *direct neuronal effect* of the cytokine. Former electrophysiological studies verified the presence of IL-1β-sensitive neural cells in the lateral hypothalamus (LHA) and in the VMH. Furthermore, in our

extracellular single cell recordings, neurons were described in the globus pallidus (GP), the orbitofrontal cortex (OBF) and the NAcc that specifically changed their activity in response to the microelectrophoretic administration of IL-1β [31,42,61].

It is often observed in the daily medical practice that infections, inflammatory processes and the development of tumors are accompanied with the loss of appetite, reduced food intake, elevated body temperature and impaired energy balance. Taken all of these into consideration, studying the central regulatory mechanisms of IL-1β in the above mentioned homeostatic processes seems to have special significance.

The NAcc, found in the basal forebrain, is proved to play an essential integrative role in the central regulation of feeding. Several neurotransmitter (dopamine, noradrenaline, acethylcholine, glutamate, GABA, opiate, histamine) mediated mechanisms are assumed in the background of the regulation of hunger motivated behavior organized in this brain area. Furthermore, it has extended connections with other regions of the limbic forebrain system which also have roles in the homeostatic control, such as the HT, GP and the prefrontal-orbitofrontal cortical areas [22,67]. In the recent years, IL-1β mediated complex homeostatic effects were confirmed in the above mentioned areas by our research group [31,43,62].

The complex mechanisms taking part in the regulation of homeostasis contribute to the integrative processing of endogenous signals and exogenous information as well. In addition to the visual, acoustic and thermal stimuli, the two exogenous chemical modalities, smell and taste play a decisive role in the regulation of feeding. Our present thesis deals particularly with the theme of taste perception.

In the recent decades several publications revealed the important role of the VMH and the NAcc in the central control of taste perception [5,54]. However, considering the neuronal and humoral background of the CNS mechanisms responsible for taste perception, our knowledge is still insufficient, especially as far as the two limbic forebrain structures under consideration are concerned.

It was, therefore, reasonable to examine whether this cytokine can influence the feeding and metabolic processes in the accumbens. It was also studied if there was a cytokine induced change in the taste perception which essentially determines the food intake of the animals.

It was revealed in former investigations that IL-1β microinjection into the VMH causes significant anorexigenic and adipsogenic effects [35]. To elucidate the possible taste perception disturbances behind these changes was also aimed in our experiments.

II. Experiments

1. Aims and questions

Our research project related to the doctoral thesis had several directions. First, the possible direct neuronal effect of IL-1β was tested on the neural cells of the nucleus accumbens by means of the multibarreled microelectrophoretic single cell recording technique. The glucose sensitivity of the neurons was also examined to elucidate if the glucose-monitoring neurons in this structure are the neural substrate of the cytokine effect.

In a second series of experiments, which was the main direction of our research project, we aimed to verify the effects of IL-1β microinjection into the nucleus accumbens on homeostatic, behavioral and metabolic processes. The short- and long-term food intake (FI), water intake (WI) and body temperature (BT) were measured before and after the microinjection of IL-1β into the nucleus accumbens. The results were compared with the findings of vehiculum treated control animals. Metabolic measurements were also performed in all groups of animals after the cytokine administration. The effects of intracerebral microinjection on glucose (in a glucose tolerance test /GTT/), cholesterol, triglyceride, HDL, LDL, uric acid, insulin and leptin concentrations of the plasma were measured. The influence of intraaccumbens IL-1β microinjection on taste perception was investigated in a conditioned taste aversion (CTA) paradigm and in a taste reactivity test.

Concerning data in the relevant literature, prostaglandin mediated biochemical reactions may have some role in the regulatory functions of IL-1β in the CNS [53]. These processes can be investigated by the inhibition of the cyclooxygenase enzyme which plays a key role in the prostaglandin biosynthesis. For this reason, in some animals a pretreatment with paracetamol, a potent inhibitor of the enzyme was performed: prior to the intracerebral application of IL-1β, paracetamol was microinjected into the NAcc of the rats. This was followed by the FI, WI and BT measurements.

In the third part of our research project, we aimed to explore the possible taste perception disturbances in the background of the profound homeostatic changes developing after the intrahypothalamic microinjection of the cytokine. The methods of the CTA and taste reactivity tests were exactly the same in the case of the animals receiving either intrahypothalamic or intraaccumbens IL-1β microinjection.

The present experiments were performed to answer the following questions:

I. In electrophysiological experiments, using the multibarreled microelectrophoretic technique, it was examined
   1. whether IL-1β has a direct neuronal effect on the NAcc neurons,
   2. if the activity of these IL-1β sensitive cells change in response to micro-electrophoretic application of glucose so they are proved to be elements of the GM network.

II. In behavioral studies, we aimed to investigate whether the bilateral microinjection of IL-1β locally into the NAcc results in alterations of
   1. food intake,
   2. water intake and
   3. body temperature.

III. In further behavioral experiments, the influence of the intraaccumbens and intrahypothalamic IL-1β microinjection on gustatory functions were explored:
   1. it was tested whether a cytokine induced conditioned taste aversion is found in the background of the characteristic behavioral changes, and
   2. in taste reactivity tests if there is any difference between the taste perception of IL-1β treated and control animals.

IV. In our metabolic experiments we investigated whether IL-1β microinjection into the NAcc influences the
   1. blood glucose level,
   2. plasma level of metabolites such as cholesterol, triglycerides, HDL, LDL and uric acid, and
   3. plasma level of insulin and leptin, two hormones playing crucial role in the humoral control of homeostasis.

2. Methods

2.1. Animals

Altogether 202 adult male Wistar rats with an average body weight of 250-290 g at the beginning of the experiments were used in our study. The animals were kept in separated, individual cages. Tap water and laboratory chow food were ad libitum available for the animals. In

the animal room, 12-12 hours long light-dark cycle was employed with an illumination close or identical to that of the wavelength of the natural light (daytime: 06-18 h). Constant room temperature (23 ± 2 °C) and humidity (45 ± 5%) were assured. Rats were handled daily during the course of the experiments to avoid stress.

2.2. Electrophysiological experiments

2.2.1. Surgery

The microelectrophysiological experiments were performed under urethane anaesthesia. The head of the rats, placed in a stereotaxic instrument, was fixed and a small hole was drilled through the cleaned skull. The electrode was led to the accumbens by means of a hydraulic microdrive under microscopic control. According to the rat brain atlas of Pellegrino et al., the stereotaxic coordinates of the extracellular single neuron recordings were as follows: anteroposterior (AP), Bregma (B) + 3.2-3.7 mm; mediolateral (ML), 1.2-1.6 mm; ventral (V, from the surface of brain) [50].

2.2.2 Extracellular single neuron recordings

For extracellular single neuron recording, tungsten wired multibarreled glass microelectrodes, manufactured by ourselves, were used. Extracellular action potentials of the neurons were recorded by the tungsten wire containing central barrel of the electrode. The 8-10 tiny capillaries that surrounded the central barrel were used to deliver the various chemicals to the vicinity of the recorded neuron.

The extracellularly recorded action potentials were passed into a preamplifier, then to a “high gain” amplifier. Analogue signals were led to a microprocessor controlled A/D converter device. The spike discharges and pulses were continuously monitored on oscilloscopes. Raw data, formed pulses and marker signals were all fed into a computer and stored on hard disk and compact disks for offline analyses. Our system enabled us to record and analyze ECG and respiration as well. Data were processed by Spike2 software package.

2.2.3 Neurochemical examinations - Taste stimulation

The capillaries surrounding the central barrel of the tungsten wired multibarreled glass microelectrodes were filled with the following solutions: 0.15 mM IL-1β, 0.5 M D-glucose, 0.5 M monosodium-L-glutamate, 0.5 M dopamine HCl, 0.5 M noradrenaline, 0.5 M acethylcholine HCl, 0.5 M γ-amino-butiric acid and 0.15 M NaCl. Microelectrophoretic applications were performed by delivering constant currents of appropriate polarity to eject the chemicals from their respective barrels.

During the recording experiments, the taste responsiveness of neurons was also examined by taste stimulations via an intraorally implanted cannula. In accordance with the international standards, the following taste solutions were tested: sweet (sucrose; 0.1M and 0.3M), salty (NaCl; 0.1M and 0.3M), sour (HCl; 0.01M and 0.03M), bitter (QHCl; 0.001M and 0.003M) and umami (MSG; 0.1M and 0.3M). As complex taste orange juice (10% and 25%) was used.

2.3. Behavioral and metabolic experiments

2.3.1 Surgery

The guide cannulas that enabled the targeted intracerebral microinjection were implanted during a stereotaxic operation performed under ketamine-diazepame (Calypsol, Seduxen) anaesthesia according to the Pellegrino rat brain atlas [50]. In case of the NAcc the coordinates were as follows: anteroposterior (AP): Bregma + 3.6 mm, mediolateral (ML): 1.3 mm. The appropriate coordinates of the VMH were AP: Bregma + 0.2 mm and ML: 1.0 mm. The cannulas were placed bilaterally right above the NAcc or the VMH on the surface of the dura mater, and were cemented to the skull by dental acrylic. Animals taking part in the taste reactivity test were additionally intraorally implanted by a polyethylene (PE) tube (outer diameter: 1.4 mm) later serving as taste cannula.

2.3.2. Nucleus accumbens and ventromedial hypothalamus microinjection

Stainless steel microinjection cannulas with a 0.3 mm outer diameter were connected via a 10-12 cm PE tube to a Hamilton syringe and led through the guide cannula to the targeted brain areas. The ventral coordinates were 5.75 mm in the case of the NAcc, and 9.5 mm in case of the VMH. The Hamilton syringe was filled with one of the following solutions: IL-1β (5 ng/μl;

dissolved in sterile phosphate buffer solution /PBS/ with 0.1% bovine serum albumin); paracetamol (3 μg/μl; or 15 μg/μl dissolved in sterile PBS); or sterile PBS alone. Drug solutions were injected by a microinfusion pump in a volume of 0.75 μl into both sides of the brain over a 60 s time interval. The injected amount of IL-1β was 3.75 ng unilaterally. The intraaccumbens administration of paracetamol, as a pretreatment, was followed by a 25 min waiting period separating it from the IL-1β microinjection.

2.3.3. Behavioral experiments

Food and water intake

In these experiments 4 groups were organized for the various NAcc microinjections which had the same mean body weight: control (CO; PBS alone), smaller dose of paracetamol (CO+P1), interleukin-1β (IL-1) and interleukin-1β with pretreatment of smaller dose of paracetamol (IL-1+P1). In an other experiment two groups of rats were formed: higher dose of paracetamol: (CO+P2) and interleukin-1β with pretreatment of higher dose of paracetamol (IL-1+P2). Drug infusions were performed on the microinjection days between 17:00 and 18:00 p.m..

Food and water, except the deprivation periods before the day of the experiment, were available *ad libitum*. On the experiment day, which was preceded by 24 h food deprivation, animals received the laboratory chow after the drug infusions at 18:00, at the beginning of the dark period. The measurements of food and water intake took place at 20:00 (2 h, short-term consumption) and on the next day morning at 6:00 a.m. and evening at 18:00 p.m. (12 and 24 h long-term consumptions).

Body temperature

Body temperature was measured under the behavioral experiments at the same time with the food and water intake measurements in the same animal groups (CO, CO+P1, IL-1, IL-1+P1 and CO+P2, IL-1+P2). Body (core) temperature was measured rectally within 0.1 °C accuracy by digital thermometer. Temperature measurements took place at 18:00 (0 h), as well as at 20:00 (2 h).

Conditioned taste aversion

Conditioned taste aversion (CTA) is the further avoidance of a food or fluid with a specific taste, which, after its first consumption, caused gastrointestinal discomfort. If the administration of a definite taste (conditioned stimulus) is paired with a treatment which results in a gastrointestinal disease (unconditioned stimulus) we can study the influence of this treatment on the acceptance of the food or fluid with the specific taste in a conditioned learning paradigm. Animals assigned for the CTA experiment first learned to consume the daily amount of their water intake at the same time from 10:00 to 10:30 a.m. every day. On the pairing day (one week after the surgery), a novel taste solution - 0.1 % Na-saccharin dissolved in tap water - was offered 30 min prior to intraaccumbens or intrahypothalamic microinjection of IL-1β or PBS. This conditioning procedure was followed on subsequent days by thirty minutes water drinking for one week. On the test day, 7 days after the microinjection, the saccharin solution was offered again exactly at the same time (from 10:00 to 10:30 a.m.). The consumptions of cytokine treated and control animals measured on the pairing and the test day were statistically compared.

Taste reactivity test

The taste reactivity test allows the characterization and quantitative evaluation of mimic, postural and locomotory movement patterns induced by pleasant and unpleasant tastes. Solutions used for taste stimulations represented the five basic tastes in two concentrations: sweet, sucrose (0.05 and 0.5 M); salty, sodium-chloride (NaCl 0.05 and 0.5 M); sour, hydrogen-chloride (HCl 0.03 and 0.3 M); bitter, quinine-hydrochloride (QHCl 0.03 and 3.0 mM) and umami, monosodium-L-glutamate (MSG 0.05 and 0.5 M). An adapted and modified version of the protocol introduced by Grill and Norgren [21] was used in our laboratory, which is acknowledged internationally. The animals were placed into a Plexiglass cylinder of 30 cm in diameter and 30 cm height. The cylinder was placed on a wooden frame mounted by a mirror in a 45° tilted angle. This enabled the easy observation of the mouth movements of the rat throughout the whole testing period. The behavior and taste responsiveness of the rats were videotaped and later analyzed frame by frame (40 ms/frame). The PE cannula, implanted into the oral cavity and fixed on the skull of the animal, was connected to a 2.25 m long PE tube (outer diameter 3 mm), and this cannula was interconnected with the syringe placed in the infusion pump and filled by the appropriate gustatory stimulus solution. Response patterns of videotaped behaviors of animals were evaluated based on frame by frame analysis. The ingestive and aversive mimical reactions and movement patterns were scored according to the character, number, order and intensity of their elements. Both ingestive and aversive behavioral patterns were evaluated in an arbitral scale from 0 to 3. The taste reactivity

indices were determined by dividing averaged sum of scores with the value of maximum possible scores.

2.3.4. Metabolic measurements

In our metabolic measurements the influence of nucleus accumbens IL-1β microinjection on carbohydrate, protein and fat metabolism was examined. Insulin and leptin serum levels were also determined.

Blood glucose level measurements

Blood glucose level measurements were performed after the administration of IL-1β or PBS in the acute and sub-acute (4 weeks after the drug infusions) phase of the experiments, after a 24 h food deprivation in a glucose tolerance test (GTT). In the acute GTT an intraperitoneal injection of D-glucose dissolved in distilled water (0.2 g/100 g bw/ml) was performed at the 10th min following the microinjection into the nucleus accumbens. The blood glucose levels, from blood samples of the tail vein of the rats, were measured using a glucometer based on an enzymatic-photometric method. Blood samples from each animal were taken right before (so-called fasting glucose level) and after the sugar load, and at the 9th, 18th, 30th, 60th, and 120th min, respectively.

Measuring plasma concentrations of metabolites and hormones

Important metabolic parameters such as total plasma cholesterol, triglyceride, HDL, LDL, and uric acid concentrations were measured by an automated biochemical analyzer using a dry chemistry system. Insulin and leptin levels were determined by ELISA method, in a collaboration with the Institute of Immunology and Biotechnology of Pécs University Medical School. Blood samples were taken following decapitation of the animals 15 min after the intraaccumbens IL-1β or vehicle microinjections. These experiments were also preceded by 24 h food deprivation.

2.4. Histology

After the electrophysiological and behavioral studies histological analyses were performed for the exact localization of the site of recording and IL-1β microinjection. Animals with inappropriate or greatly asymmetrical cannula or electrode positions or with expanded tissue damage were excluded from further analysis.

2.5. Data analysis

One-way and repeated measures analysis of variance (ANOVA) and the Tukey's and Student-Newman-Keuls test were employed for post hoc comparisons. Differences were considered to be significant at the level of $p<0.05$ or less. The SPSS for Windows software package was used for the statistical analysis of behavioral and metabolic experiments. In the statistical analysis of the results of the electrophysiological experiments Student-*t* and χ^2-tests were used.

3. Results

3.1. Electrophysiological findings

In our extracellular single cell recordings, IL-1β sensitivity of 25 neurons was examined. Twelve neurons changed their activity in response to the microelectrophoretic application of the primary cytokine, 8 of them were facilitated, and 4 were inhibited. Six out of the 12 cytokine sensitive neurons also responded to microelectrophoretic application of glucose, 4 of them were facilitated, so proved to be so called glucose-receptor cells, and 2 were inhibited, thus, proved to be so called glucose-sensitive cells. The responsiveness of IL-1β sensitive neurons to neurotransmitters was also tested: cytokine sensitive neurons showing responsiveness to glutamate, GABA, dopamine, and noradrenaline were identified in the NAcc. In addition to testing endogenous chemosensitivity, the exogenous chemosensitivity to intraoral gustatory stimuli was also examined in the cytokine sensitive neurons: out of the 12 cells that showed responsiveness to IL-1β, 6 changed firing rate to gustatory stimuli and 3 of them were glucose-monitoring (GM) neurons as well.

3.2. Changes in food and water intake

Food intake

The direct bilateral microinjection of IL-1β into the NAcc proved to be anorexigenic for the animals. The short-term food intake (food consumption of the first 2 h after the microinjections) of the cytokine treated rats was reduced significantly compared to that of the control rats, regardless of

whether it was performed with or without the paracetamol pretreatment. The low-dose paracetamol microinjection did not prevent development of the IL-1β induced anorexia. The paracetamol per se or microinfusion of the control solution (PBS) did not affect short-term food intake. In contrast to the difference among cytokine treated and control rats in the short-term food intake, the long-term (12 h) food consumptions of the groups did not differ significantly. Increasing the dose of paracetamol did not influence the anorexigenic effect of the cytokine. Those animals, that were infused with the higher dose of paracetamol before the IL-1β treatment, consumed significantly less, than those that - as a control group - were injected with the higher dose of the COX-inhibitor.

Water intake

The intraaccumbens microinjection of IL-1β resulted in adipsia in the rats. Short-term water intake of the cytokine treated rats was significantly lower compared to that of controls, and the paracetamol pretreatment did not influence this adipsogenic effect. The lower dose of paracetamol microinjection did not prevent the development of the IL-1β induced adipsia. The paracetamol per se or microinfusion of the control solution (PBS) did not affect short-term water intake. In contrast to the difference among cytokine treated and control rats in the short-term water intake, the long-term water consumptions of the groups did not differ significantly. The higher dose of paracetamol did not prevent the adipsogenic effect of the cytokine as well. Those animals, that were infused with the higher dose of paracetamol before the IL-1β treatment, drank significantly less, than those that - as a control group - were injected with the higher dose of the COX-inhibitor.

3.3. Body temperature

The microinjection of IL-1β into the NAcc was followed by a significant elevation of body temperature. The low dose paracetamol pretreatment in the NAcc did not affect the development of hyperthermia, it could not prevent the IL-1β induced febrile response. In the long-term body temperature measurements we did not find significant differences among the groups. In contrast to the food and water intakes, which remained unchanged, the intraaccumbens microinjection of higher dose of paracetamol could prevent the pyrogenic effect of IL-1β. Body temperatures of animals obtaining P2, then IL-1β remained at physiological level, as well as those of P2 then PBS microinjected rats.

3.4. Metabolic changes

3.4.1. Blood glucose levels

Pathological alterations of blood glucose levels, and a definite glucose intolerance of the cytokine treated animals became obvious in this experiment. The acute GTT started 10 min after the bilateral intracerebral microinjection of either IL-1β or PBS solution. Already from the time preceding the i.p. glucose load blood glucose levels of the two groups appeared to be different from each other. Blood glucose concentrations of the cytokine treated animals were significantly higher than those of control rats during the whole experiment. In the sub-acute phase (4 weeks after the treatments), no significant difference was found during the GTT in the blood glucose levels between the IL-1β and CO groups, blood glucose curves of both groups remained at physiological level.

3.4.2. Plasma levels of metabolites

The triglyceride, total cholesterol, and LDL levels of cytokine treated animals were significantly higher than those parameters of control rats. HDL and uric acid concentrations of the two groups did not show a significant difference.

3.4.3. Plasma levels of hormones

15 min after the microinjection of IL-1β into the NAcc the insulin plasma level of the cytokine treated animals was significantly higher than those parameters of control rats. In contrast, no substantial difference was found between the values of the two groups in the case of leptin levels.

3.5. Taste perception disturbances in the nucleus accumbens

3.5.1. Conditioned taste aversion

The role of IL-1β mediated mechanisms in the NAcc in the processing of taste-related information and integrating with adaptive behavior was first studied in a conditioned taste aversion

paradigm. The microinjection of IL-1β into the NAcc did not cause a conditioned taste aversion in the animals.

3.5.2. Taste reactivity

Characteristic changes in reactivity patterns were observed after the microinjection of IL-1β into the NAcc during the application of both pleasant and unpleasant taste stimuli. Pleasant taste stimuli elicited significantly less ingestive responses in the IL-1β treated animals than in the controls. Furthermore, cytokine injected rats showed significantly less aversive patterns to unpleasant taste stimuli than the PBS infused ones. In contrast to the controls, the intensity of the ingestive responses of IL-1 treated animals to pleasant and unpleasant tastes was the same. The remarkable disturbance in evaluation of unpleasant tastes were shown in cytokine treated animals: the intensity of ingestive and aversive patterns to hedonically negative taste stimuli did not differ from each other.

3.6. Taste perception disturbances in the ventromedial hypothalamus

3.6.1. Conditioned taste aversion

Direct bilateral IL-1β microinjection into the VMH did not cause the development of conditioned taste aversion. In the saccharin taste aversion paradigm, there was no significant difference in the pairing and test day consumptions of rats of the IL-1β treated and control groups.

3.6.2. Taste reactivity

Findings of the taste reactivity tests revealed characteristic gustatory deficits of the cytokine treated rats. These disturbances were apparent regarding the hedonically positive, pleasant tastes. The IL-1β treated rats gave significantly poorer ingestive reactions to pleasant taste stimuli than did animals of the control group. The aversive responses of IL-1β injected rats to these pleasant tastes were significantly stronger than those of control animals. The substantial disturbance of the hedonic judgement of tastes was further demonstrated by the fact that following intrahypothalamic interleukin administration the cytokine treated animals showed stronger aversion than ingestion to hedonically positive tastes. Considering the unpleasant, aversive taste stimuli, the taste-elicited

responses did not differ in hedonic quality among the groups: both the control and cytokine treated animals displayed overwhelmingly aversive reactivity patterns to these tastants.

4. Discussion

Our complex behavioral-metabolic and electrophysiological series of experiments revealed significant role of IL-1β mediated processes in the regulation of feeding, taste perception, and metabolism in the NAcc and the VMH, two structures in the limbic forebrain having important functions in the homeostatic control.

The electrophysiological findings verify the existance of IL-1β sensitive neurons in the NAcc. Although cytokine sensitive neurons already have been shown and characterized in the HT, OBF, and several other structures of the limbic forebrain, our recent findings are the first that prove the direct neuronal effect of IL-1β in the NAcc.

Our behavioral-metabolic series of experiments, which represent the main part of the doctoral thesis, showed profound and multiple homeostatic alterations such as decrease of food and water intake, raise of body temperature, characteristic taste perceptional disturbances, and complex metabolic changes after the bilateral microinjection of IL-1β into the NAcc. Although the homeostatically relevant mechanisms observed after the peripheral or cerebral administration of the cytokine were described in several reports, so far, however, we had no experimental data about the IL-1β processes in the NAcc that fundamentally alter central regulation of feeding, taste perception, and metabolism.

Although involvement of the VMH in taste perception was widely debated in literature, the possible contribution of taste associated perceptual and motivational processes to the IL-1β induced anorexia has gained relatively little attention so far. Our knowledge was insufficient about the possible gustatory changes after the direct intrahypothalamic administration of the cytokine. The results in the conditioned taste aversion and taste reactivity tests, therefore, contribute to a better understanding of the taste perception alterations in the background of the anorexigenic and adipsogenic effects of IL-1β injected into the VMH.

4.1. IL-1β mechanisms in the limbic forebrain

The presence of IL-1β and its receptors in different brain regions that participate in the control of homeostasis indicate that this primary cytokine acts directly on the CNS [1]. By using

autoradiographic techniques, IL-1 receptors were detected in the hypothalamus and the nucleus accumbens as well [15]. Furthermore, variations in the diurnal rhythm of mRNA of IL-1β were demonstrated in both the HT and the NAcc in other molecular biological studies [7].

In extracellular single neuron recordings, we have identified neurons in the NAcc that changed their firing rate in response to microelectrophoretic application of IL-1β suggesting a direct neuronal effect of the cytokine in this forebrain structure [61]. In previous investigations, IL-1β responsive neurons with specific, feeding-associated neurochemical sensitivities were described in various parts of the limbic forebrain, in structures intimately involved in the control of food and fluid intake and metabolism, such as the OBF, VMH, LHA, and the GP [31,42,44]. The NAcc is known to have strong interconnections with these and other forebrain sites already shown to be involved in central feeding control [23]. Considering all the above, it is reasonable to suppose that this cytokine mediated central neural circuitry, including the IL-1β processes in the nucleus accumbens, possess an important integrative role in the maintenance of homeostasis.

4.2. Food and water intake

Numerous works have demonstrated that peripheral and central administration of IL-1 results in a decrease of food intake [31,43,53]. To date, however, IL-1β mediated processes in the NAcc, considered as being intimately involved in the central control of feeding, have not been published yet. In our present findings, the robust decrease of food intake was present even despite the 24 h food deprivation, causing a high hunger motivation state, and this underlines the regulatory power and the physiological importance of the accumbens cytokine mechanisms.

The present data demonstrate a remarkable hypodipsia after the IL-1β microinjection into the NAcc. Although several studies indicate a direct action of the cytokine in the CNS to suppress water intake, the mechanism of this effect remains to be elucidated [52]. However, it was reported that suppression of food and water intake after i.c.v. injection of the cytokine is mediated by different receptors: anorexia, but not adipsia, is mediated by IL-1 receptor type I (IL-1RI) [58]. Other mechanisms may also be involved, and this is indicated by the fact that in our study water deprivation was not applied before the treatments, and also that no difference was observed in the long-term consumptions of the cytokine treated and control animals.

4.3. Body temperature

Direct microinjection of IL-1β into the NAcc caused a significant rise of body temperature. Similar findings were reported previously after both peripheral and central administration of the primary cytokine [31,41,43]. This is the first time, however, when pyrogenic effect of IL-1β administration is described in the NAcc. Although our knowledge about the thermoregulatory roles of NAcc is still insufficient, single unit recordings have already identified thermosensitive neurons here [10]. In our study, the febrile response, and the anorexigenic and adipsogenic effects were observed at the same time. Previous reports suggested that the behavioral and pyrogenic effects of the cytokine are mediated by distinct receptor subtypes [34], and there are data indicating that the central effects of low dose of IL-1β on body temperature are mediated by IL-1RII in the brain [40]. Nevertheless, the induction of CRF also seems to be an important element of the IL-1β induced fever [55], and the activation of the central catecholaminergic system may be involved as well [47]. Recently, differential mechanisms of the hyperthermic and anorexigenic action of IL-1 were further substantiated by demonstrating an active role of the central melanocortin system in IL-1 mediated anorexia, but not in hyperthermia [38].

4.4. Influence of paracetamol on the IL-1β elicited homeostatic alterations

Prostaglandin mediated mechanisms appear to participate in the homeostatic effects induced by IL-1 since pretreatment with cyclooxygenase inhibitors - at least partially - could block these alterations [24,66]. In our experiments the microinjection of both doses of paracetamol into the nucleus accumbens did not influence the cytokine elicited anorexigenic and adipsogenic effects and its lower dose did not prevent hyperthermia as well. After the application of higher dose of the COX-inhibitor, however, the significant rise of body temperature was not observed, which refers to the involvement of prostaglandin mechanisms in the IL-1β induced pyrogenic effect in the NAcc. In a previous report it was also described that ibuprofen injected into the third ventricle could not block the central anorexigenic effect of the cytokine, but on the other hand, the rise of body temperature was prevented [56]. Nevertheless, i.c.v. administration of the drug results in less specific effects, whereas a microinjection given to a definite brain region offers the possibility to demonstrate the role of prostaglandin mediated mechanisms in the IL-1β induced homeostatic processes in the NAcc.

4.5. Metabolic changes

The results of our experiments demonstrate that complex metabolic alterations develop as a consequence of the bilateral accumbens microinjection of IL-1β. In addition to a diabetes-like impaired glucose tolerance, plasma triglyceride, total cholesterol and LDL levels increased in the cytokine treated animals. The influence of either peripherally or centrally administered cytokines on glucose metabolism has been demonstrated in several studies [8,37]. The interpretations, however, seem to be contradictory. It was reported that i.c.v. administration of IL-1β stimulates glycogenolysis and thus elicits hyperglycemia [59]. Others emphasized the decrease of blood glucose level after the injection of IL-1 into the lateral brain ventricle [11]. However, in our study, a well-defined brain region, which was already described to be involved in the control of metabolism, was targeted by a precise microinjection of the cytokine.

Our present data demonstrate characteristic metabolic alterations after the administration of IL-1β into the NAcc. According to several studies, a variety of cytokines can affect multiple processes altering lipid metabolism. In certain infections, the cytokine induced increase of serum lipoprotein levels may be a beneficial response to the host, since lipoproteins can bind and neutralize endotoxins and viruses [16]. Furthermore, IL-1 has been suggested to modulate directly lipid metabolism by suppressing the activity of lipoprotein lipase [14], and by inhibiting the synthesis of fatty acid transport proteins in adipose tissue [20]. Based on our recent data, the elevated plasma level of triglycerides, TC and LDL in the cytokine treated animals might refer to an IL-1β mediated neural mechanism directly affecting the peripheral lipid metabolism. However, the metabolic pathways influenced by these immuno-neuroendocrine interactions remain to be elucidated.

Plasma concentration of insulin was shown to be significantly higher in the cytokine treated rats compared to the controls after the IL-1β microinjection into the NAcc. The influence of either centrally or peripherally administered IL-1β on insulin level was reported by several studies [8,59]. Low dose of the primary cytokine injected intracerebroventricularly elicits hyperinsulinemia but after the application of higher doses this effect cannot be observed [59]. The exact mechanism is unknown, the cytokine induced decrease of the glycogen production of the liver and the increase of glyconeogenesis may be involved, and the developing hyperglycemia increases insulin level which is later restored to physiological level by other processes. IL-1β injected into the NAcc did not cause an alteration in the leptin levels. Nevertheless, our knowledge about the interactions of the IL-1β and leptin neural systems in the homeostatic regulation is constantly growing. It was shown that IL-1β mediates the hyperthermic and food intake decreasing effects of the centrally

administered leptin [39], and it was also demonstrated that i.v. injection of leptin enhances the expression of IL-1β in the hypothalamus, which is inhibited by glucocorticoids [25].

4.6. Taste perception alterations

The anorexigenic and adipsogenic effects observed after the bilateral microinjection of IL-1β into the NAcc were not due to a cytokine elicited conditioned tate aversion. The taste reactivity tests, however, revealed apparent taste perception disturbances, namely a characteristic deficit of response patterns appeared in the IL-1β treated animals after both pleasant and unpleasant taste stimulations.

A learned aversion was not shown in the background of the food and fluid intake decreasing effect of the IL-1β administration into the VMH as well. However, our findings demonstrated characteristic alterations of the gustatory responsiveness of rats after the intrahypothalamic administration of IL-1β. Taste perception disturbances substantially differ from the experienced alterations in the NAcc, because in the case of the VMH primarily complex changes relating to the responses to pleasant tastes were shown. After the cytokine microinjection into the VMH, the animals displayed significantly poorer ingestive and stronger aversive reactivity patterns to pleasant gustatory stimuli compared to the controls.

Peripheral (i.p.) or central (i.c.v.) administration of the cytokine has already been reported to elicit CTA [27,64], nevertheless, there are also data available for the lack of CTA after similar treatments [3,64]. Despite the debates, the literature is in general in favor of limited importance of learned aversion, even if it develops, in the hypophagia induced by IL-1β [3]. Our related investigations were the first to address this question after direct intraaccumbens and intrahypothalamic application of the cytokine, and the findings provided clear evidence for that microinjection of a low dose of IL-1β into the NAcc and the VMH is not followed by the development of CTA, i.e., a cytokine induced aquired aversion does not contribute to the anorexic symptoms seen after such treatments.

Although immune system activation is already well-known to interfere with the hedonic judgement of various taste qualities, the apparent difficulties in the interpretation of results of previous investigations may originate in the methodological differences and the diversion of application sites and manners of the cytokine [2,9]. In our case bilateral microinjection of the primary cytokine was performed directly into the VMH or the NAcc, and afterwards the adapted and internationally acknowledged modified version of the classic taste reactivity test developed in

our laboratory was applied, which enables us to thoroughly reveal the taste perception changes after the intracerebral drug administrations [21].

4.7. Neuronal background of the homeostatic control

The various homeostatic effects seen after the intracerebral application of IL-1β have already demonstrated the physiological importance of complex, multiple regulatory processes, which are, at least partially, mediated by this primary cytokine. Our recent experiments provide the first evidence for characteristic behavioral and metabolic changes as a consequence of a direct bilateral administration of IL-1β into the NAcc [62] and the VMH [60]. Our knowledge about the neural circuitry, which takes part in the central control of homeostasis and is assisted by several neuropeptides, neurotransmitters and cytokines acting at various levels of the brain and the periphery, expands constantly. The involvement of local serotonergic, dopaminergic and noradrenergic mechanisms in the IL-1β mediated homeostatic processes were revealed after the intrahypothalamic application of the cytokine [57]. Further investigations indicated that pretreatment with the nitric oxide precursor L-arginine prevents the increase of intrahypothalamic serotonin level and hypophagia caused by i.c.v. administered IL-1β [26]. Another important homeostatic neuronal system, the neuropeptide Y network is also interconnected to the IL-1β mediated neural mechanisms: i.c.v. microinfusion of IL-1β induces the production and release of components of the IL-1β system and decreases mRNA levels of neuropeptide Y simultaneously in the hypothalamus [18].

Early electrophysiological studies provided evidence for the existance of glucose-responsive neurons in the VMH and LHA, that display specific firing rate changes in response to alteration of the extracellular glucose concentration [45,46]. Since then, similar glucose-monitoring neural cells have already been identified in several structures of the rodent and primate brain, including the ventrolateral and mediodorsal prefrontal cortex, globus pallidus and the NAcc [29,30,33,49]. Electrophysiological data suggest that IL-1β exerts a direct neuronal effect on certain elements of this hierarchically organized GM network, and by affecting this neural circuitry, it influences various aspects of homeostatic functions [36,42]. The GM neurons represent one third of all neural cells in the VMH, and it is known that high proportion of these chemosensory units change in activity in response to IL-1β [36,48]. Furthermore, the cytokine sensitive GM neurons - not only in the VMH but in other representation sites of the central GM neural network as well (LHA, GP, OBF, NAcc) - have also been shown to be modulated by gustatory stimuli [32,33,63].

Considering the intimate involvement of these chemosensory cells in the organization of feeding behavior, it is plausible to hypothesize that IL-1β elicited activity changes of GM neurons in the VMH resulted in the shifts of responsiveness of these animals to palatable tastes [33,45]. A cytokine elicited activation of the VMH "satiety center", i.e., a consequent enhanced satiation can, therefore, be supposed in the background of the hedonic shift [60]. Neverheless, it is worth noting that glucose-insensitive cells here, though in lower proportion, do also change in firing rate in response to IL-1β, thus, their contribution to these gustatory alterations cannot be excluded at all [36]. Chemosensory neurons changing their firing rate to intraoral gustatory stimuli are also present in the NAcc [49], and taste-responsive neurons that also showed activity change to microiontophoretically applied IL-1β were also shown in this structure [63]. Our extracellular single neuron recordings verified direct neuronal effect of IL-1β on GM and glucose-insensitive cells in the NAcc [61]. It is, therefore, reasonable to suppose that IL-1β mediated adaptive reactions organized in the nucleus accumbens and the ventromedial hypothalamus exert their multiple homeostatic effects partly via the modulation of the central GM network and partly via various other complex, "immunocrine" neural systems.

III. General conclusions

According to our findings, microinjection of IL-1β into the NAcc significantly influenced the food and fluid intake behavior, regulation of body temperature, resulted in characteristic taste perception deficit, and complex disturbances of carbohydrate and fat metabolism as well. In case of the VMH, our research group revealed similar alterations in former investigations and our recent results emphasize the importance of taste perception changes and the shift of hedonic judgement in the background of these fundamental food and water intake disturbances. All these findings suggest that IL-1β mediated processes of the NAcc and the VMH - structures having essential roles in the control of feeding and metabolism - are intimately involved in the central regulation of homeostasis. The examined brain regions are incorporated in a hierarchically organized control system, and it seems that their dysfunction can lead to the upset and thoroughly disturbance of the balance of homeostasis.

Alimentary and metabolic disorders cause increasing public health problems for the modern societies due to the growing incidence of these diseases. Feeding and metabolic diseases such as diabetes mellitus, metabolic syndrome and obesity have become endemic in the present days. Although their therapies have shown tremendous progress in the last decades, a resounding success, a real breakthrough cannot be experienced in their treatment. One reason for this, perhaps, that the

emphasis so far was put on the investigation of only the peripheral alterations in these disorders. The most important conclusion of our results is the hypothesized dysfunction of the central regulation in the above mentioned disorders, in which the functional disturbances of the NAcc and the VMH may play a pivotal role.

Considering all of the above, we hope that the extensive functional investigation of CNS structures, such as the NAcc and the VMH, can lead to completely new experimental results which will subsequently influence the preclinical and clinical studies and the development of more successful therapeutic strategies in these feeding and metabolic diseases.

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Publications

I. Papers

A. Publications related to the thesis

Takács G., Papp Sz., Lukáts B., Szalay Cs., Nagy B., Fotakos D., Karádi Z. Homeostatic alterations after IL-1β microinjection into the nucleus accumbens of the rat. *Appetite* 54 354-362. 2010.
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B. Further publications

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II. Books, chapters, proceedings

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III. Abstracts

A. Abstracts published in international journals

Lukáts, B., Papp, Sz., Juharosi, Gy., Ságodi, L., Takács, G., Szalay, Cs. and Karádi, Z.: Homeostatic disturbances after intrahypothalamic IL-1β microinjection. Ideggyógyászati Szemle (Clinical Neuroscience) 56(2): 55, 2003.

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