Glucose-monitoring neurons in the mediodorsal prefrontal cortex

Ph.D. Thesis

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I. Introduction

The incidence of feeding and metabolic disorders is worldwide quickly increasing. These diseases - obesity, anorexia and bulimia nervosa, diabetes mellitus and metabolic syndrome - dramatically contribute to the significant increase of the morbidity and mortality rates in the modern societies. The importance of these pathological conditions is outstanding with respect to public health issues, and it is also worth noting that little is known about complex physiological-pathophysiological processes in the background, and consequently the efficacy of our therapeutic efforts is still very much restricted.

Characteristic homeostatic imbalance can be detected in metabolic and feeding disorders. To an adaptive control of feeding and metabolism, not only the adequate perception of environmental stimuli, but the integrity of complex neural and neurochemical-humoral regulatory processes assuring stability of the internal milieu is also essential. The revealing of these homeostatically relevant regulatory processes is aimed nowadays by extensive research all over the world.

The prefrontal cortex (PFC) is one of the key cortical structures to monitor the internal state of the organism and to initiate behavioral outputs accordingly. The PFC is implicated in many regulatory processes, including cognitive functions, attention, drive and motivation, decision making and working memory [1-3]. Food and fluid intakes are also known to be regulated by the PFC. Bilateral lesions of the medial PFC result in finickiness, but failed to induce major feeding alterations, while ventral-lateral PFC damages lead to the development of aphagia [3].

Anatomically, the PFC is situated in the anterior pole of the mammalian brain reportedly having reciprocal interconnections with the mediodorsal thalamic nucleus. The term of mediodorsal prefrontal cortex (mdPFC) is used for neuroanatomical subdivisions of the PFC such as the prelimbic and cingulate cortices.

The prefrontal cortex is considered to perform its complex roles via multiple interrelationships with forebrain and brainstem areas. Anatomical studies have shown that the medial-mediodorsal prefrontal cortex has direct connections with limbic structures, such as the amygdala (AMY), the lateral hypothalamic area (LHA), the nucleus accumbens (NAcc) and the adjacent orbitofrontal cortex (OBF) [4-6], all known to be important in the central feeding control. The rat mdPFC also directly projects to the nucleus of the solitary tract

(NTS), a brainstem region which integrates a number of autonomic reflexes [7] and is known as a key structure of the central taste information processing [8, 9] as well.

In previous studies, special chemosensory cells, the so-called glucose-monitoring (GM) neurons, have been discovered in the above interconnected regions [10-13]. These GM neurons display firing rate changes in response to elevation of blood glucose level or to local microelectrophoretic administration of D-glucose. A majority of the GM neurons also show responses to intraorally delivered taste stimuli [11, 14-16]. These homeostatically relevant, taste-sensitive GM neurons are suggested to form a complex hierarchically organized neural network integrating endogenous and exogenous information to control food and fluid intake and metabolic processes [11, 14, 16].

The GM cells were demonstrated to be influenced by catecholamines [11, 16, 17], and with respect to this, it is especially important to note that the PFC is the major cortical target area of the ascending mesocorticolimbic dopamine (DA) projections [18-21]. In addition to responding to various endogenous chemical stimuli, these chemosensory neurons of the hierarchically organized network are also known to integrate multiple, homeostatically relevant information, such as exogenous chemical and other signals that are associated with sensory-motor, perceptual, motivational mechanisms, as well as reinforcement, learning and memory processes of the homeostatically adaptive control of feeding and metabolic functions [10, 11, 15, 16, 22].

Considering the above, it is supposed that the mediodorsal prefrontal cortex accomplishes its complex roles as integrant part of the forebrain glucose-monitoring neural network. In a series of the present experiments, therefore, we aimed to identify GM neurons in the mdPFC, and to examine their responsiveness to DA.

Streptozotocin (STZ) is known to selectively destroy β-cells of the pancreatic Langerhans-islets, and correspondingly, it is widely used to induce experimental type 1 diabetes mellitus in animals [23, 24]. STZ enters the cell via glucose transporter type 2 (GLUT2) and causes alkylation of DNA. The cytotoxic action of STZ is mediated by reactive oxygen species [24]. Furthermore, previous studies have also reported that intracerebral microinjection of streptozotocin can specifically destroy the GM neurons of various brain areas (eg. ventromedial hypothalamus, orbitofrontal prefrontal cortex and globus pallidus) causing severe deficits of feeding, inducing taste perception alterations, and metabolism [14, 16, 25-27].

The other line of the present experiments, on the one hand, was therefore, designed to evaluate taste associated behavioral-cognitive consequences of bilateral streptozotocin

microinjection into the mdPFC of rats in a conditioned taste avoidance (CTA) acquisition paradigm (the long term avoidance of specifically tasting food or fluid after pairing it with gastrointestinal discomfort), as well as during taste reactivity tests.
On the other hand, it was also reasonable to examine the animals' glucose tolerance (in glucose tolerance test; GTT), and the change of plasma metabolite concentrations after bilateral streptozotocin microinjection into the mdPFC.

II. Experiments

1. Aims and questions

In previous experiments it was demonstrated that the glucose-monitoring neural network has particular significance in the adaptive regulation of feeding. No data is available, however, about the presence of glucose-monitoring neurons in the homeostatically relevant mediodorsal prefrontal cortex.
In the present experiments, therefore, we aimed to identify GM neurons in the mdPFC, and, after isolating them, to examine their complex functional characteristics. Extracellular single neuron activity of the mdPFC of anesthetized rats was recorded by means of multibarreled glass microelectrodes during 1) microelectrophoretic administration of D-glucose and DA, 2) intraoral gustatory stimulations, and 3) intragastric infusions of chemicals.
In other series of experiments, to elucidate the homeostatic significance of mdPFC GM neurons, we aimed to investigate the effects of STZ microinjection into the mdPFC on feeding associated taste information processing and metabolic functions.

In this study we aimed to answer the following questions:

I. In microelectrophysiological experiments, using the multibarreled microelectrophoretic technique, it was examined:

1. Are there GM neurons (special chemosensory cells changing their activity to microelectrophoretic administration of D-glucose) present in the mediodorsal prefrontal cortex?

2. How do the glucose-monitoring neurons and the glucose-insensitive ones change in firing rate to dopamine, a neurotransmitter known to be important to mediate relevant physiological processes of the mdPFC?
3. Are there taste sensitive neurons in the mdPFC? Is there any difference between the taste sensitivity of the GM units and that of the glucose-insensitive neurons?
4. Is the discharge rate of the mdPFC neurons influenced by intragastric chemical stimulations?

II. Behavioral experiments to explore the effect of STZ microinjection into the mdPFC on taste information processing:

1. Does selective destruction of the GM cells modify taste avoidance learning?
2. Does selective lesioning of the GM neurons elicit any taste reactivity deficit?

III. Metabolic effects of local intracerebral microinjection of STZ:

1. Does selective destruction of the GM cells cause glucose intolerance, i.e. alteration of carbohydrate metabolism?
2. Does the specific lesion of these chemosensory neurons exert any effect on relevant plasma metabolite levels (cholesterol, HDL, LDH, triglycerides, uric acid)?

2. Methods

2.1. Animals

Altogether 168 male Wistar and 23 Sprague-Dawley rats with an average body weight of 268-380 g were used in our experiments. Rats were housed in a temperature and light controlled room (21 ± 2 °C; 12-12 h light-dark cycle) where constant humidity (55-60%) was also assured. The animals were kept in individual cages and they were handled in daily regularity. Tap water and laboratory chow food were ad libitum available for the animals, unless where it is stated different. All experimental procedures were conducted in accordance with institutional, national and international regulations.

2.2 Electrophysiological experiments

2.2.1. Surgery

Anesthetized rats were operated on stereotaxically, their scalp was incised, and a small hole was drilled through the skull. The microelectrode was led to the mdPFC under microscopic control through the incised dura by means of a hydraulic microdrive (Narishige MO-10, Japan). The stereotaxic coordinates for electrode placements in the mdPFC were chosen according to the rat brain atlas [28]: anteroposterior, bregma + 3.2-4.0 mm; mediolateral, 0.7-1.6 mm; vertical, 0.6-2.8 mm.

2.2.2. Extracellular single neuron recording

Extracellular single neuron recording and microelectrophoretic application of neurochemicals were accomplished by means of nine-barreled glass microelectrodes. The single neuron activity was recorded via the central barrel of the microelectrode containing a tungsten wire (10 μm in diameter, impedance 1.5-8 MΩ at 50 Hz). Neurochemicals were applied electrophoretically through the capillaries surrounding the central recording barrel. Constant current source (NeuroPhore BH-2 System, USA), producing constant currents (in the 5-95 nA range) of appropriate polarity, was applied to eject the neurochemicals from their respective barrels. Extracellular action potentials were passed into a preamplifier, a high gain amplifier including low and high cut filters and a window discriminator to form standard pulses (Supertech Ltd., Hungary), and then, into a microprocessor controlled A/D converter device (CED 1401 plus). The Spike 2 software package (Cambridge Electronic Design Ltd., United Kingdom) was used to construct frequency histograms, and for real-time and off-line analyses. Neuronal spikes and formed pulses were continuously observed on oscilloscopes. Only the action potentials of spontaneously active, well-isolated cells were recorded. Similar to our previous studies, a neuron was considered to be responsive to a certain neurochemical if its firing rate changed by at least ±30% or by ±2 SD from the mean baseline level, and if the reactions were dose dependent (different response magnitude by using different current intensities), and replicable.

2.2.3. Neurochemical examinations and taste stimulations

The capillaries surrounding the central barrel of the tungsten wired multibarreled microelectrode were filled with one of the following solutions: D-glucose (0.5 M, pH 7.0), dopamine hydrochloride (0.5 M, pH 6), and monosodium L-glutamate (0.5 M, pH 7-8; to test the electrode tip's vicinity to the recorded neuron) and 0.15 M NaCl.

The gustatory responsiveness of mdPFC neurons was examined by injection of various taste solutions via an intraorally positioned cannula. Solutions of the five primary qualities and orange juice as a complex taste were tested: sweet (sucrose; 0.1M and 0.3M), salty (NaCl; 0.1 and 0.3M), sour (HCl; 0.01M and 0.03M), bitter (QHCl; 0.001M and 0.003M), umami (MSG; 0.1M and 0.3M) and orange juice (10% and 25%).

Effect of intragastric infusions on activity of mdPFC neurons was also examined. NaCl (60 mM and 150 mM), D-glucose (60 mM) and MSG (60 mM) were injected by an infusion pump into the stomach via a polyethylene tube (volume: 3 ml; flow rate: 0.3 ml/min).

2.3 Behavioral and metabolic experiments after STZ microinjection

2.3.1 Surgery

Stainless steal guide cannulas (23 G) were carefully lowered and placed on the surface of the dura above the mdPFC by a fine mechanical microdrive (MN-33 Narishige, Japan) under ketamine anesthesia. After positioning, the guide cannulas were fixed to the cranium using dental acrylic and anchoring screws. Microinjection cannulas (30 G) were passed through these guide cannulas to deliver the chemicals directly to the mdPFC. Stereotaxic coordinates for mdPFC according to the stereotaxic rat brain atlas of Pellegrino et al. [28] were: AP: +3.7 mm anterior to bregma (B), ML: 1 mm, and V: 1.5 mm (from dura).
Animals taking part in the taste reactivity test were also implanted with chronic intraoral taste cannula made of polyethylene (PE) tube (o.d. 1.33 mm). Each taste cannula was placed lateral to the first maxillary molar and was transbuccally tunneled subcutaneously to ascend lateral to the skull.

2.3.2. STZ microinjection

Rats were microinjected bilaterally with 7.5 µg STZ (Sigma S-0130, 10 µg/µl; dissolved in sterile physiological saline) or sterile physiological saline alone in a volume of 0.75 µl for one minute. Solutions were microinjected by a microinfusion pump (Cole Parmer 789200C) into the mdPFC (V: 1.5 mm from the brain surface) through a stainless steal injection cannula (o.d. 0.3 mm) extending 1.5 mm below the tips of the guide cannula fixed on the skull with dental acrylic.

2.3.3. Behavioral experiments

Conditined taste avoidance

In the CTA test, animals were put on a 30-min drinking schedule and learned to consume the daily amount of their water intake from 10:00 to 10:30 a.m. every day. On the pairing day (four days after the microinjection of STZ or physiological saline) animals had access to 0.1 % Na-saccharin for 30 min, and 30 min later they were injected i.p. with lithium chloride (0.15 M, 20 ml/kg b. w.), a gastrointestinal (and other vegetative) malaise inducing drug. After this conditioning procedure, animals had water available for 3 days in the 30-min schedule. On the 4th (test) day, water was replaced by saccharin in the drinking period. The consumptions of saccharin solution measured in the STZ treated and control groups on the pairing and test days were statistically compared.

Taste reactivity test

The taste reactivity tests characterizing and evaluating mimic, postural and locomotor patterns induced by the pleasant and unpleasant tastes, were conducted according to the modified, internationally accepted protocol of Grill and Norgren [29-32]. Rats with intraoral taste cannulas were given a 7-day habituation period during which they were daily placed into a Plexiglass cylinder of 30 cm in diameter and 30 cm in height, where intraoral water infusions were regularly made. The taste reactivity tests were performed 7 days after the STZ microinjection.

The animals were given two concentrations of taste solutions representing the five basic tastes: 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, QHCl (0.03 and 3.0 mM); and umami, monosodium-L-glutamate (MSG, 0.05 and 0.5 M). With the help of a microinfusion pump (Cole Parmer 789200C), 0.5 ml of taste solution was infused into the mouth of the animal at a constant rate (0.5 ml/min) for one minute. After the infusion of a taste solution, the taste cannula was rinsed with distilled water and blown through by air. Based on previous reports [33, 34], both concentrations of sucrose and the lower concentrations of NaCl and MSG were regarded as pleasant tastes, while both concentrations of HCl and QHCl and the higher concentrations of NaCl and MSG were considered as unpleasant taste stimuli.

The behavior of rats was recorded by digital video camera and later analyzed frame by frame. A mirror in a 45° tilted angle was mounted on a wooden frame enabling observation of the rat's mouth during the test. Mimical and postural-locomotor responses were scored using an adapted and modified version of the protocol introduced by Grill and Norgren [29, 32]. Ingestive actions were characterized by rhythmic mouth movements, rhythmic tongue protrusions along the midline, lateral tongue movements and paw licking. Aversive behavioral patterns were gaping, chin rubbing, head shaking, forelimb flailing and rapid locomotion around the cylinder. The species specific response patterns of the STZ treated and control animals were judged by 3 independent, experienced examiners, and the obtained data of the two groups were finally compared and statistically analyzed.

2.3.4. Metabolic experiments

The standardized glucose tolerance test (GTT) was performed after a 12 h food deprivation of the rats. Intraperitoneal injection of 20% D-glucose solution (0.2 g/100 g bw/ml) was administered at the 20th min following the intracerebral microinjection of STZ or saline (acute GTT) and then 4 weeks later (subacute GTT).

Relevant plasma metabolites (total cholesterol, HDL, LDH, triglycerides, uric acid) were determined 30 min after the STZ or saline microinjection by a cold chemistry photometer (Spotchem EZ SP4430, Arkray, Japan).

2.4. Histology

After finishing the electrophysiological and behavioral studies, histological analyses were performed to examine the location of the tip of microelectrodes or the microinjection

sites. Animals with inappropriate electrode or cannula positions were excluded from further analysis.

2.5. Statistics

For statistical analysis of data of the electrophysiological experiments, the Wilcoxon test, Kruskal-Wallis test, linear regression test, and $\chi 2$ test were used. Results of behavioral and metabolic studies are reported as means ± SEM**.** One-way analysis of variance (ANOVA) and the Tukey's test for post hoc comparisons were used for statistical analysis. Differences were considered to be significant at $p<0.05$.

3. Results

3.1. Microelectrophysiological experiments

3.1.1. Glucose and dopamine responsiveness of mdPFC neurons

Activity changes of altogether 272 neurons have been recorded in the Wistar and Sprague-Dawley rat mdPFC. The mean spontaneous firing rates: 2.2±0.2 and 2.4±0.3 spikes/s, respectively, did not vary significantly between the two rat strains. Sixty-two (24.3 %) of 255 mdPFC neurons showed responsiveness to glucose, thus, these cells were identified as elements of the forebrain GM neural network. The predominant response to glucose was inhibition (43 of the 62 GM neurons, 69.4 %), however, facilitatory activity changes were also detected (19 /30.6 %/ of the 62 neurons). The other 193 neurons (75.7 %) did not change in firing rate to glucose and thus, were classified as glucose-insensitive (GIS) cells.

DA responsiveness of altogether 235 cells was examined in the rodent mdPFC. Microiontophoretic application of DA resulted in activity changes of 55 neurons (23.4%). Proportion of the excitatory (28, 11.9%) and inhibitory (27, 11.5%) responses was almost the same.

Twenty-one (41.2%) of the 51 GM units, whereas only 27 (16.2%) of the 167 GIS neurons displayed discharge rate changes to this neurotransmitter, so that DA responsiveness of the GM cells was found to be significantly higher than that of the glucose-insensitive units

($p<0.001$; $\chi 2$ test). DA elicited only excitatory response in the GR cells (7 of 15 neurons, 46.7%), whereas both inhibitory (10 of 36 units, 27.8%) and excitatory (4 of 36 cells, 11.1%) firing rate changes were observed in the GS neurons. Consequently, direction of the DA induced activity changes of the two types of GM cells differed significantly ($p<0.01$; $\chi 2$ test). The magnitude of the response to microelectrophoretically administered glucose and DA was also examined. In both cases, higher current intensities elicited significantly bigger firing rate changes of cells of the responsive groups ($p<0.05$; Wilcoxon test).

Baseline firing rates and spike durations of the neurons with distinct glucose and DA responsiveness did not differ significantly ($p=0.248$ and $p=0.30$, respectively; Kruskal-Wallis test). In addition, neither baseline firing rates nor spike durations were found to correlate with glucose or dopamine responses ($p \geq 0.213$).

3.1.2. Effects of intraoral and intragastric stimulations

In addition to testing endogenous chemosensitivity (to neurotransmitters and neuromodulators), the exogenous chemosensitivity, in this case, gustatory responsiveness was also tested in 259 mdPFC neurons. Almost half of the tested cells (49.4 %) showed taste responsiveness to at least one of the five taste qualities. The proportion of taste sensitive GR units was 80 % (16 of 20), but in case of GS and GIS neurons it was only less than 50 %. Majority of the taste sensitive neurons changed their activity to two or more tastants.

When the effect of intragastric infusions on mdPFC neuronal activity was examined, 45 % of the tested neurons showed activity changes to 60 mM NaCl (34 of 76), 39 % (27 of 70) to 150 mM NaCl, 41 % (35 of 85) to 60 mM D-glucose and 51 % (38 of 75) to 60 mM MSG solutions.

3.2. Behavioral experiments

Conditioned taste avoidance

Bilateral STZ microinjection into the mdPFC did not impair the acquisition of LiCl induced saccharin CTA. The CTA developed in the STZ treated and also in the control animals, that is, the intakes of the testing day were much lower than those of the pairing day in both groups (ANOVA, $F_{3,85} = 14.161$; $p < 0.001$). The same efficacy of gustatory learning

was also substantiated by the fact that there was no significant difference in the saccharin consumptions of the two groups on the testing day (Tukey's test, p=0.298).

Taste reactivity test

Bilateral microinjection of the STZ induced alterations of reactivity to various taste stimuli. The taste reactivity tests revealed characteristic gustatory deficits in case of administration of pleasant taste stimuli (ANOVA, $F_{3,35}$=19.451; p<0.001). The ingestive responses of STZ treated animals to pleasant taste stimuli were significantly poorer than those of the control rats (Tukey's test, p<0.05). Considering the aversive (rejection) patterns to pleasant tastes, the STZ treated animals and also the control rats gave similar amount and intensity of aversive reactions to these tastants. Taste reactivity deficit of STZ treated animals to pleasant taste stimuli was the most obvious in case of the higher concentration of sucrose and the lower concentration of NaCl solutions.

As far as the unpleasant gustatory stimuli are concerned, there was no significant difference in the unpleasant tastes elicited ingestive and aversive responses between the STZ treated and control animals.

3.3 Metabolic changes

Glucose tolerance test

Pathological alterations of blood glucose levels and a definite glucose intolerance of the STZ treated animals became obvious in the acute GTT. Two hours after the i.p. injection of the glucose solution, blood glucose level of the STZ treated animals was significantly higher than that of the rats in the control group (control: 6.95 mmol/l ± 0.14 mmol/l, STZ 8.6 mmol/l ± 0.51; p < 0.05).

In the subacute phase, there was no significant difference between the blood glucose concentrations of rats of the STZ treated and control groups, and the blood glucose curves of both groups remained in the physiological range throughout the test.

Plasma levels of metabolites

Total cholesterol, HDL, LDH and uric acid plasma concentrations of the STZ treated and control groups did not show any significant difference. At the same time, however, significantly decreased plasma triglyceride levels were detected in the STZ microinjected animals.

4. Discussion

The prefrontal cortex (PFC) is defined as the cortex of the anterior pole of the mammalian brain, predominantly receiving projections from the mediodorsal thalamic nucleus [4, 35]. It has been demonstrated that the prefrontal cortex is implicated in many regulatory processes, including cognitive functions, decision making, working memory, and the control of motivated behaviors such as the food and fluid intake [3, 5, 36-40].
The prefrontal cortex is considered to perform its complex roles via multiple interrelationships with forebrain and brainstem areas. Anatomical studies have shown that the medial-mediodorsal prefrontal cortex has direct connections with limbic structures, such as the AMY, the LHA, the NAcc and the adjacent orbitofrontal cortex (OBF) [4-6], all known to be important in the central feeding control. The rat mdPFC also directly projects to the NTS, a brainstem region which integrates a number of autonomic reflexes [7] and is well-known as a key structure of the central taste information processing [8, 9] as well.

Endogenous chemical responsiveness of mdPFC neurons

In previous investigations, a particular type of chemosensory cells, the so-called glucose-monitoring (GM) neurons - displaying firing rate changes in response to elevation of blood glucose level or to local microelectrophoretic administration of D-glucose - have been discovered in the above interconnected brain areas. Specific glucose-inhibited (glucose-sensitive, GS) neurons were identified in the LHA of rats [12, 41] and later in the LHA and the AMY of rhesus monkeys [10, 11, 42], in the area postrema, in the globus pallidus [17, 43] and in the NTS, too [43, 44]. By contrast, the NAcc and the OBF were proven to contain not only GS cells but also glucose-excited (glucose-receptor, GR) neurons that are facilitated by

increase of the extracellular glucose concentration [13, 16]. Only GR cells were found in the VMH.

Results of the present experiments provided evidence for the existence of glucose-monitoring neurons in the mediodorsal prefrontal cortex. The mdPFC is known to be involved in a broad variety of regulatory processes, and its important role in the central feeding control has been demonstrated as well [3, 5, 37, 45]. It is important to note that the previous results have been obtained predominantly in the macaques whereas the present study was performed in the rodent. Nevertheless, findings of the latter gain more general significance in the light of our most recent microelectrophysiological experiments in the alert rhesus monkey revealing that GR and GS neurons also exist in the primate mdPFC (unpublished data).

As the other major finding of the present experiments, differential dopamine sensitivity of the mdPFC neurons has been elucidated: the feeding-associated GM cells were shown to be more likely to change in activity in reponse to microiontophoretically administered DA than the glucose-insensitive units. Furthermore, the GR neurons were found to get facilitated whereas the GS units mainly inhibited by this catecholamine. These data are in concordance with previous results demonstrating higher dopamine responsiveness of the lateral hypothalamic and pallidal GM neurons compared to that of the GIS cells, as well as the predominance of DA induced inhibitory firing rate changes of the GS neurons in the LHA [11, 17].

The dense dopaminergic innervation of the PFC [18-21] has already been indicated to play important roles in a variety of regulatory processes [1, 46-51], including feeding-associated and taste mediated learning and memory mechanisms as well [36, 52-54]. It is especially worth noting here that food intake itself or stimuli associated with the food have been demonstrated to increase the extracellular DA concentration in the prefrontal cortex [55, 56]. These and our present data are also in agreement with the notion that multiple regulatory functions of the mdPFC are perfectuated via interrelated complex neurochemical mechanisms [40, 51].

Previous recording studies have suggested that cortical interneurons have shorter spikes than the pyramidal neurons, though it has also been shown that the cortical pyramidal neurons may exhibit a wide variety of spike durations [57-59]. In our study, examination of spike durations revealed no significant difference among the various groups of neurons, and spike durations also did not correlate with glucose and dopamine responses.

Exogenous chemical responsiveness

A diet of an organism is greatly determined by the perceived palatability of foods. Accordingly, the gustation plays distinguished role in the choice of foods and fluids. In the ordinary series of events, nutritional chemoreception is followed by adaptive feeding behaviors and consequent homeostatic changes.

The existence of taste responsive neurons in the mdPFC was proven in our study. Activity changes of mdPFC neurons to both intraoral and intragastric chemical stimulation were recorded. The proportion of taste sensitive GR units was significantly higher than that of the taste sensitive GIS neurons. Consequently, GR neurons in mdPFC may have special importance in specific mechanismus of the high level gustatory information processing.
There are important humoral (e.g. serotonin, GLP-1) and neural (activation of vagus nerve afferents) interrelationships between the gastrointestinal system and the central nervous system to contribute to the taste perception and recognition processes [60-62]. Expression of sweet, bitter and umami receptors in the intestinal tract has been demonstrated [63-65]. Recent fMRI studies showed the cerebral effect of intragastrically administered taste solutions (D-glucose, MSG, NaCl) [66]. Our finding of neuronal activity changes during intraoral or intragastric taste stimulations support the postulated functional interrelationships between the relevant regulatory mechanisms of the mdPFC and the pre- and postabsorptive processes of the gastrointestinal tract.

Since GM neurons of several brain areas have already been shown to be indispensable constituents of integration of endogenous and exogenous chemical information, sensory-motor, perceptual and motivational processes, as well as reinforcement, learning and memory mechanisms of the regulation of food and fluid intake behaviors [10-13, 15-17, 22], it is reasonable to suppose that these chemosensory cells of the mdPFC possess similar complex functional attributes in the organization of adaptive feeding actions.

Conditioned taste avoidance

It has been proven in the present study that bilateral STZ microinjection fail to impair taste avoidance learning in a saccharin conditioned CTA paradigm. Results of the present experiments are in agreement with previous data, where animals with mediodorsal or dorsolateral PFC ablations were not impaired in CTA learning [45, 67]. There are also data available, however, that microiontophoretically applied neurotoxins (kainic acid and 6-

hydroxydopamine) in the medial prefrontal cortex cause significant deficits in CTA acquisition and retention [53]. Discrepancies among the findings probably rise from the different cell specificity of the microdamages, because STZ causes selective destruction of the GM neurons only. Previous experiments provided evidence for that STZ microinjection into the NAcc leads to CTA deficit in rats [14]. In the present experiment, we failed to detect similar changes after STZ microinjection of mdPFC indicating that not all parts of the GM neural network are involved in CTA aquisition. Consequently, our results suggest that the GM neurons of the mdPFC are not essential to associate the taste of ingested food with delayed noxious consequences of the ingestion of it tested in a CTA paradigm.

Taste reactivity tests

The present study revealed taste reactivity deficit of rats after bilateral STZ microinjection into the mdPFC. The STZ treated animals displayed significantly poorer ingestive reactions to pleasant taste stimuli than did rats of the control group. The taste reactivity changes were the most pronounced in the case of sweet and salty taste stimulations. The underlying neural mechanism of these symptoms is supposed to be the selective cytotoxic effect of STZ on the GM neurons. A single bilateral microinjection of the STZ into either the VMH or the OBF induced specific destruction of the local GM neurons resulting in development of complex metabolic and feeding disturbances [16, 25], also including characteristic taste reactivity alterations [14]. Selective damage of GM neurons in the OBF caused significantly stronger aversive reaction to pleasant tastants and more ingestive patterns to unpleasant tastes. Based on that the mdPFC is an integrant part of the forebrain glucose-monitoring neural network as well as on previous and our recent observations, it is reasonable to suppose that GM neurons of the mdPFC play similar complex functional roles in integratory processes of the adaptive feeding actions.

Although it has been shown that chronic decerebrate rats executed both ingestion and rejection response sequences similar to those observed in controls [30], we suppose that the lack of inputs of certain taste-responsive cortical neurons may cause palatability shift. Our hypothesis is in agreement with previous findings proving that rats with gustatory cortex lesions failed to display aversive reactivity to LiCl-paired tastants in a taste reactivity test [68]. A possible neural background of our findings might be the lack of appropriate mdPFC input to thalamus, since the thalamus appears to be essential in mimetic responses associated with ingestion [30]. In our experiment, deficit of the ingestive patterns might be due to a GM

cell destruction induced imbalance of complex homeostatic and hedonic processes of food and fluid intake behaviors.

Metabolic changes

In the present study evidence was obtained for the intimate involvement of mdPFC GM neurons in the central regulation of metabolism.

In our body, the central nervous system takes part in the control of metabolic processes by means of integrating metabolic (fatty acids, ketone bodies, lactic acid, other metabolits), humoral-hormonal (e.g. insulin, leptin, GLP-1) and complex neural information coming from various brain structures and from the periphery [69-71] as well.

Among patients with type 1 diabetes mellitus, associations between metabolic control measures and prefrontal cortical thickness deficits were examined [72]. Long-term glycemic control levels were found to be associated with thickness reduction in the bilateral superior prefrontal cortical regions.

The results of our studies show that complex metabolic alterations develop as a consequence of bilateral mdPFC microinjection of STZ. Selective destruction of GM neurons leads to diabetes-like impaired glucose tolerance and altered triglyceride level.

The present findings support our hypothesis that the GM neural network play essential role in the preservation of homeostatic balance. Damage to these chemosensory neurons may elicit and maintain complex feeding and metabolic diseases.

5. General conclusions

Feeding and metabolic disorders like diabetes mellitus, metabolic syndrome and obesity cause increasing public health problems in the modern societies. The presently used therapeutic approaches concentrate on targeting the peripheral pathology, and so far they could not reach a breakthrough.

Our present findings support the view that dysfunction of the regulatory processes of CNS should necessarily to be taken into consideration in the above mentioned diseases. Our results, along with previous data, indicate a clear overlapping of the endogenous and exogenous chemosensory systems in the mdPFC. Especially the GM neurons here appear to

integrate complex chemical information of various sources, which predestinate them to play significant adaptive role in the central regulation of feeding and metabolism.

Considering all of the above, we hope that the better understanding of complex functional attributes of mdPFC neurons and those of other brain structures important in the maintenance of homeostasis, can lead to new drug targets and the discovery of successful new therapeutic strategies.

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Publications

I. Papers

A. Publications related to the thesis

Nagy B., Szabó I., Papp Sz., Takács G., Szalay Cs., Karádi Z.:
Glucose-monitoring neurons in the mediodorsal prefrontal cortex
Brain Research 1444:38-44. 2012.
IF: 2.728

Nagy B., Takács G., Szabó I., Lénárd L., Karádi Z.:
Taste reactivity alterations after streptozotocin microinjection into the mediodorsal prefrontal cortex
Behavioural Brain Research 234: 228-232. 2012.
IF: 3.417

B. Other publications

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.
IF: 2.433

Takács G., Szalay Cs., **Nagy B**., Szabó I., Simon D., Berki T., Karádi Z.:
Insulin and leptin plasma levels after the microinjection of interleukin-1β into the nucleus accumbens of the rat
Acta Physiologica Hungarica 99 (4), 472-478. 2012.
IF: 0.821

II. Abstracts

A. Abstracts published in international journals

Karádi Z., Takács G., Szalay Cs., **Nagy B.**, Papp Sz., Lukáts B., Lénárd L.: Complex homeostatic attributes of the forebrain glucose-monitoring neurons
Appetite**,** 51:(2) 376- p., 2008.

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Clinical neuroscience (Ideggyógyászati szemle) 65(S1): 62. 2012.

B. Other presentations

G. Takács, **B. Nagy**, Cs. Szalay, D. Fotakosz, Sz. Hanna, M. Mizuno, K. Narikiyo and Z. Karádi: Taste perception deficit after interleukin-1β microinjection into the nucleus accumbens of the rat
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12th Meeting of the Hungarian Neuroscience Society, Budapest, 2009.

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Cseténvi B., Hormay E., Szabó I., **Nagy B.**, Hideg B., Faragó B., Bajnok Góré M., Karádi Z.: Endogén és exogén kémiai ingerek hatása az umami-érzékeny idegsejtekre patkány cinguláris kérgében
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