Role of the ventromedial prefrontal cortex in taste related learning and hedonic mechanisms

Ph.D. thesis

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1. INTRODUCTION

The medial prefrontal cortex of rat can be devided in terms of citoarchitectonic characteristics, neural connectivity and functions into dorsal and ventral parts [1]. The dorsal part (includes anterior cingulate cortex and dorsal part of the prelimbic cortex) maintains dense connections with somatosensory and motor systems. The ventral part, namely the ventromedial prefrontal cortex (vmPFC) consist of the ventral part of prelimbic cortex and the infralimbic cortex. It has extensive connectivity with the limbic and association cortical areas and has been implicated in several higher-order functions such as reward, memory, emotion, attention, planning, executive function and in autonomic control. The vmPFC has reciprocal connections with feeding associated gustatory and hedonic impact coding structures as well (e.g. lateral hypothalamus, amygdala, insular cortex, nucleus accumbens, orbitofrontal cortex) [2, 3]. The vmPFC is densely innervated by catecholaminergic fibers originating from hindbrain and midbrain [4]. Dopaminergic projections (mesocortical dopamine system) to the vmPFC arise predominantly from A10 cells of the ventral tegmental area (VTA) and innervate densely the vmPFC [5]. Noradrenergic innervation originates from the A6 cell region in the locus coeruleus [6]. Electrophysiological study evidenced that neurons of the vmPFC are responsive to taste stimuli and they are involved in the hedonic representation of tastants [7, 8]. Consumption of highly palatable food enhances both dopamine and noradrenaline extracellular concentration in the vmPFC [9, 10]. Optogenetic studies suggested that activation of DA-1 dopaminergic receptors in vmPFC leading to increased intake of highly palatable foods [11]. Several data in the literature indicate the involvement of both catecholaminergic neurotransmitters also in taste associated learning processes (conditioned taste aversion) in other brain regions (e.g. nucleus accumbens, lateral hypothalamus, basolateral amygdala) [12-14], but their possible role in the vmPFC is not known. Human functional imaging studies detected dysfunction and atrophy in Br 25 and Br 32 areas (which are homologue regions to the vmPFC of rats) [15] in eating disorders and obesity [16-18]. Furthermore, these individuals displayed alterations in hedonic evaluation of taste stimuli as well. In view of these data, it is reasonable to hypothesize that vmPFC might be involved in hedonic evaluation of tastes and in taste related learning and memory processing.

The main goal of the present study was to investigate the involvement of local neurons of vmPFC and their catecholaminergic innervations in the hedonic regulation of feeding and food selection, and in taste related learning and memory processes. Therefore, kainate or 6-hydroxydopamine (6-OHDA) lesions were performed in the vmPFC. Kainate destroys neuronal cell bodies intrinsic to the area where it is applied, while passing fibers remain unaffected [19]. 6-OHDA damages catecholaminergic fiber terminals resulting in retrograde degeneration of projection neurons [20]. Neurotoxins were applied by iontophoretic method to minimize the extent of lesion and the side effects (enhances epileptic activities, disturbances in motor capabilities and autonomic functions, aphagia, adipsia, regulatory deficits in response to distinct physiological challenges or hypokinetic symptoms) [21, 22].

2. OBJECTIVES

The aim of the present study was to investigate the functional deficit in feeding related behaviors after damage of neurons or catecholaminergic inputs in vmPFC. With this design we examined the consequence of lesions:

1) in the homeostatic body weight control

2) in the regulation of food intake

3) and in ad libitum water intake.

4) Furthermore, we examined the involvement of vmPFC in the adaptation mechanism to physiological challenges (i.p. injection of 0.15 M or 1 M NaCl solution).

5) According to literature data and previous studies, large lesions of the whole mPFC or catecholaminergic lesions of dmPFC result in hyperactivity. In our experiments, we investigated the effect of iontophoretic microlesion of vmPFC in the regulation of general and stereotyp activity.

6) Our research group has previously found that dopaminergic lesion of dmPFC increased glucose preference. In the present study, we assessed the preference of two

sweet taste with distinct energetic values (glucose and saccharin) following vmPFC lesions.

7) In view of our results, we are interested in, whether the altered taste preference may have been caused by the damage of hedonic evaluation of tastes. To study this, taste reactivity tests were performed with different tastants following vmPFC lesions.

8) Furthermore, we investigated the involvement of vmPFC in taste associated learning mechanisms, namely conditioned taste-aversion learning processes, ie, in conditioned taste avoidance.

9) We studied the function of vmPFC in the retrieval of previously learned aversive taste informations as well.

10) The conditioned taste-aversion learning results not only in the avoidance but also in „hedonic shift" of taste. Therefore, we investigated the possible modulating effect of vmPFC lesions in the „hedonic shift" mechanism after acquisition of conditioned taste aversion. Accordingly, we applied a taste solution with high hedonic value.

3. MATERIALS AND METHODS

3.1. Subjects

298 adult male Wistar rats, initially weighing 270-340 g, were used in these experiments. Rats were housed individually and cared for in accordance with institutional (BA02/2000-8/2012), national (Hungarian Government Decree, 40/2013. (II. 14.)) and international standards (European Community Council Directive, 86/609/EEC, 1986, 2010). Animals were kept in a temperature (22 ± 1 ºC), humidity (55 ± 10 %) and light- controlled room, 12-12 h light-dark cycle with lights on 6:00 a.m. – 6:00 p.m.). Standard laboratory food pellets (CRLT/N standard rodent food pellet, Charles River Laboratories, Budapest, Hungary) were available ad libitum. The availability of drinking-water during the experiments is detailed in the subsequent sections. Rats were handled in daily regularity during the experiments.

3.2. Neurotoxic surgery

Animals were operated on under combined anesthesia consisting of intraperitoneal injection of a 4:1 mixture of ketamine (Calypsol, Richter Gedeon, 80 mg/kg body weight) and benzodiazepam (Seduxen, Richter Gedeon, Hungary, 20 mg/kg body weight, 2 ml/kg body weight of the mixture). The head of the rat was fixed in a stereotaxic device and a small (1.5-2 mm) hole was drilled through the skull above the target area. Then, the dura was opened under microscopic control. Tribarrel glass micropipettes (pulled from Pyrex glass; tip diameter: 17-25 μm) were filled with a neurotoxin and Pontamine Sky Blue [(PSB), GURR, saturated in 0.15 M NaCl and 0.05 M Na-acetate]. Kainic acid (KA, 80 mM, dissolved in distilled water, Sigma-Aldrich Co.) was used to destroy local neurons and 6-hydroxidopamine (6-OHDA, 80 mM, dissolved in 1 % ascorbic acid solution made from 0.15 M NaCl solution, Sigma-Aldrich Co.) was applied to damage catecholaminergic innervation of vmPFC. Micropipettes were carefully lowered to the target area by a hydraulic microdrive (Narishige, MN-33, Japan). Stereotaxic coordinates for vmPFC according to stereotaxic atlas [23] were: anteropostreior (AP): 3.2 mm; mediolateral (ML): 0.6 mm and (dorsoventral) DV: 4.2 mm (from dura). Kainate or 6-OHDA were iontophoretically released (5μA, 5 min) from micropipette bilaterally into the vmPFC by a constant current device (Biostim Professional, Supertech, Hungary). After ejection of neurotoxins, PSB was iontophoretized (12 μA, 4 min) to mark the location of glass pipette. Pipettes remained in place for an additional 2 min after current termination to enhance diffusion of materials from the pipette tip. In control rats 0.15 M NaCl and PSB containing pipettes were lowered to the identical target area and traced back (sham operation).

3.3. Implantation of intraoral cannulas

In the taste reactivity experiments, immediately after stereotaxical surgeries chronic intraoral (IO) cannulas were implanted in control and lesioned animals to enable the infusion of taste solutions into the mouth. The IO-cannulas were constructed of PE-100 (polyethylene) tubing. It's heat-flared end was anchored just anterolateral to the first maxillary molar and brought out subcutaneously. The other end of cannula was fitted with an L-shaped 16 mm section of 19 gauge stainless steel needle at the skull. Dental acrylic was applied to skull screws to secure the IO-cannula. The IO-infusion of taste solutions was delivered by a syringe controlled by a programmable Cole-Parmer infusion pump (Cole-Parmer, IITC, Life Sci. Instruments, California) at the rate of 0.5 ml/min. Rats were given postoperative penicillin

and were allowed to recover from surgery for 1 week before testing, during which period their cannulas were flushed with distilled water daily to prevent blockage.

3.4. Behavioral experiments

3.4.1 Body weight, food and fluid intake.

After the neurotoxical operations (CO: n=7, KA: n=7, 6-OHDA: n=7) body weight, food and water consumption were daily measured (8:00 – 8:30 in the morning) throughout the experiment.

3.4.2. Physiological challenges

When postoperative daily water and food consumption reached the preoperative level, animals (CO: n=13, KA: n=10, 6-OHDA: n=10) were exposed to physiological challenges. Firstly, physiological NaCl solution (0.15 M, 20 ml/kg body weight) was i.p. injected and the amount of 4 h, 6 h and 24 h postinjection water consumptions were measured and analysed. After 5 days recovery period intracellular dehydration was performed by i.p. injection of hypertonical NaCl solution (1 M, 20 ml/ kg body weight) and the amount of 4 h, 6 h and 24 h postinjection water consumptions were measured.

3.4.3. General activity and behavioral stereotypes in open field

Animals (CO: n=18, KA: n=15, 6-OHDA: n=16, representive) were placed in a 60 x 60 x 60 cm grey painted cage for 3 min after 3 day habituation. The bottom was divided into 16 (4 x 4 cm) identical squares. The general activity (number of crossing of squares), the behavioral stereotypes (the number of rearing, grooming, sniffing and freezing) and the number of bolus was counted.

3.4.4. Taste preference investigations using two-bottle test

Following the recovery period (CO: n=7; KA: n=6; 6-OHDA: n=7) glucose preference was tested using a 24 h free choice two-bottle paradigm. For 4 days (10-14th postoperative days) tap water and 250 mM glucose solution were available ad libitum in the home cage. Following 4 days ad lib. water intake, water and 500 mM glucose solution were available as free-choice for 4 days (18-21th days). After the 4 days ad. lib. water intake period, 10 mM saccharin and water consumptions were tested. Finally, the intake and preference of two sweet tasted sulutions with different energy value were compared: 10 mM saccharine and 500 mM

glucose. The amount of consumptions was daily measured in ml. Preference score was calculated as intake of taste solution/total fluid intake during 4 days of two-bottle test.

3.4.5. Taste reactitivity test

Chronic intraoral cannulas were implanted in 25 animals (CO: n=10; KA: n=8; 6-OHDA: n=7) to assess taste reactivity. Testing was conducted in a plexiglas test cylinder (diameter: 200 mm, height: 250 mm), which was placed on a transparent plastic floor. Underneath the test cylinder a mirror was held at a 45° angle that permitted an unobstructed view of the rat's face and ventrum. A close-up video recording of the rat's face during taste reactivity sessions was obtained with a video camera. Habituation was initiated on the 8th postoperative day and lasted for 3 days (8-10.), when the animals were placed individually in the test cylinder for 15 min without IO-infusion. After the 15 min adaptation period rats received IO-infusion of distilled water (1 ml, at a rate of 0.5 ml/min). On the 11^{th} postoperative day rats received IO-infusion of moderately concentrated taste solutions (625 mM glucose, 55 mM saccharin, 430 mM NaCl, 4,75 mM citrate, 0.625 mM quinine) to avoid the novelty effect (neophobia) of tastants. Taste reactivity was tested on the 12-16. postoperative days. In each day only one taste quality in four concentrations were tested. The applied tastants are shown in Table 1. The four concentrations of tastants were tested in ascending series. Each concentration of tastants was followed by rinsing of the rat's IO-cannula and mouth with 1 ml distilled water and flushing with 3 cm^3 air. All taste reactivity behaviors during the infusion period were scored frame-by-frame and in slow motion (1/10 and 1/25 of actual speed) by observers blind to treatments. Taste reactivity responses were scored according to the categories described by Grill and Norgren [24]. Ingestive responses consisted of the number of rhythmic midline tongue protrusions, lateral tongue protrusions and paw licking. Aversive hedonic reactions included gapes, head shaking, forelimb flailing, chin rubbing, face wiping and paw treading. Discrete actions were counted each time they occurred including lateral tongue protrusions, gapes, head shaking, forelimb flailing, chin rubbing, face wiping and paw treading. Continuous actions such as tongue protrusion, rhythmic mouth movements and paw licking were measured in secundum and then multiplied by their average frequency (6/sec), similarly as it was described by Flynn and Grill [25].

Tastant	Concentration (mM)			
Glucose	250	500	750	1000
Saccharin	1	10	100	1000
NaCl	50	100	1000	1500
Citrate	0.1	1	10	100
Quinine	0.125	0.25	1.25	2.5

Table 1. The applied taste solutions in the taste reactivity test.

3.4.6. Acquisition of CTA

In this set of experiments the ability of association between the taste stimulus and the postingestive malaise was examined after vmPFC lesions. Rats were put on a limited access to water, 30-min a day, lasting for 7 days (1st - 7th days) to habituate the animals to the 30 min drinking schedule. Animals were divided into three experimental groups and were stereotaxically operated on according to the original iontophoretic procedure on the 8th day. Altogether n=27 kainate lesioned animals, n=29 6-OHDA lesioned animals and n=30 control rats were used to test acquisition of CTA. The recovery period lasted for 8 days (9th -16th days), which included free access to water lasting for 5 days and 30-min water drinking schedule for 3 days. After reaching their preoperative (ad libitum) fluid intake during the 30 min schedule, a taste solution was offered in the regular drinking period on the 17th day. After the second presentation, when the temporary neophobia to the taste solution disappeared, a conditioning procedure was performed (18th day, conditioning day). The 30-min drinking of taste solution was followed by an i.p. injection of lithium chloride (LiCl, 0.15 M, Reanal, Hungary, 20 ml/kg b.w.t.) in 0.5 h contiguity on the conditioning day. Then animals had water available for 6 days (19th -24th days). On the 25th (Acquisition) day, water was replaced again by taste solution in the drinking period. The consumption measured on Acquisition day was registered and compared to those measured on Conditioning day. The reduction of intake on Acquisition day compared to consumption on Conditioning day was used as a measure of CTA strength [26, 27]. Four different taste qualities (50 mM NaCl, 10 mM saccharin, 10 mM citrate and 0.25 mM quinine) were used as conditioning stimuli, and each taste solution was tested in separate experiments.

3.4.7. Retrieval of CTA

In this set of experiments the retrieval of a previously learned taste information (CTA) was investigated after vmPFC lesions. Intact rats were conditioned to acquire taste avoidance (1st – 16th days) prior to surgery according to the above described CTA method. Acquisition of develpoed CTA was tested on the 16th day. For 3 days after CTA testing (17th – 19th days), animals were allowed to drink water in the 30-min schedule. On the 20th day rats were divided into three groups (kainate: n=26, 6-OHDA: n=28 and control: n=27) and were operated on according to the original procedure. Retrieval of CTA was tested following a 8-day recovery interval (21st-28th days). On the 29th day (Retrieval) water was substituted again by the taste solution in the usual drinking period. The applied taste stimuli were the same as in the first set of experiments, namely 50 mM NaCl, 10 mM saccharin, 10 mM citrate and 0.25 mM quinine. The reduction of intake during the Retrieval was compared to that of Conditioning day. This reduction was used as a measure of retrieval of the previously acquired taste avoidance [26]. The increased consumption in Retrieval compared to Acquisition was used as a measure of retrieval deficit.

3.4.8. Hedonic shift after conditioned taste aversion

During a 8 days recovery period animals ((CO: n=7; KA: n=7; n=6-OHDA: n=6) were habituated to the plexiglas cylinder (used in taste reactivity test) for 30 min/day. On the 6-8th days rats received IO-infusion of distilled water (5 ml, at a rate of 0.5 ml/min) in the last 10 min of adaptation period. On the 9^{th} postoperative day, 10 mM saccharin was injected into the oral cavity to avoid neophobia. On the conditioning day (10th day) IO-infusion of 10 mM saccharin was followed by an i.p. injection of lithium chloride (LiCl, 0.15 M, Reanal, Hungary, 20 ml/kg b.w.t.) in 0.5 h contiguity Hedonic value of 10 mM saccharin was tested after a recovery period (4 days) on the 15th postoperative day (5 ml infusion/10 min). All taste reactivity behaviors during the infusion period were scored frame-by-frame and in slow motion. To determine the hedonic value of 10 mM saccharin solution we used the method from Pfaffman: (number of ingestive responses/total responses) – (rejective responses/total responses) [28] .

3.5. Histology

At the end of experiments, animals received an overdose of urethane (2 g/kg i.p.) and were transcardially perfused with isotonic saline followed by phosphate-buffered formalin (10

%, v/v) solution. Brains were removed and frozen after 1 week of post-fixation and cut into 40 μm serial sections. For histological analysis of kainate lesions and control „sham operation", brains were stained with cresyl violet. For the identification of catecholamine depletion due to the microiontophoresis of 6-OHDA, three 6-OHDA lesioned animals were randomly selected from each experiment. Distribution of catecholamine fibers in the vmPFC was studied by immunohistochemical tyrosine hydroxilase (TH) labeling method [29]. TH immunohystochemistry was performed by means of monoclonal antibodies (Sigma, TH-16, 1:10000) against TH in the 6-OHDA animals. The brain sections of the remained 6-OHDA rats were stained with neutral red.

3.6. Statistical analysis

For statistical analysis of experimental data were computed and assessed by analyses of ANOVA (SPSS Statistics 20.0 for Windows data analysis program). Two-way repeated measures ANOVA was used for analysis of body weight, food and water intake measurements. One-way ANOVA was used to test data of physiological challenges, general activity and behavioral stereotypes, and taste preference. Data of conditioned taste aversion and taste reactivity experiments were analysed by two-way ANOVA, data of two-bottle test were tested by multifactorial repeated measures and two-way ANOVA. Comparisons among the groups or trials carried out using Bonferroni or Tukey post hoc test. Differences were considered to be significant only at the level of $p<0.05$.

4. RESULTS

4.1. Histology

After the histological staining procedure the placement and extent of lesions was checked in histological brain sections of the animals according to the stereotaxic atlas of Paxinos and Watson [23]. The placement of the lesion was correct (ventral part of the PL and whole IL) in 286 brains from the 298 brains. The tracks of the pipettes were bilaterally symmetrical. Results of cresyl-violet histological analyses showed robust cell loss in the target area in averaged with 400 μm diameter (350-450 μm, respectively) arounded with an area with 600-800 μm diameter, which showed moderate cell loss and confined well to the vmPFC. After 6-OHDA lesion loss of TH immunoreactive fibers was found in molecular (I) layer, where mainly the noradrenergic inputs of vmPFC terminates [6] as well as in deep

layers (V. and VI.), which correspond to the main terminal field of the dopaminergic inputs of vmPFC area [30, 31]. Lesion sites were verified according to the stereotaxic atlas of the rat. Data of those animals, in which lesions exceeded the boundaries of the target area were excluded (n=12) from further analysis.

4.2. *Body weight*

Two-way repeated measures ANOVA revealed that there was a significant effect of days [$F(20,360)=32.869$, $p<0.001$] and a significant effect of treatments [$F(2,18)=5.132$, $p<0.05$] with a significant interaction [$F(40,360)=6.570$, $p<0.001$]. Post hoc test showed significant body weight reduction in Kainate group from the 1st to the 7th postoperative day compared to controls (1-7th days, KA vs. CO: $p<0.01$). Bilateral 6-OHDA lesion of the vmPFC did not result significant change in body weight.

4.3. Food and water intake

Two-way repeated measures ANOVA of data of food intake revealed that there was a significant effect of days [$F(22,396)=11.212$, $p<0.001$] and a significant effect of treatments [$F(2,18)=7.151$, $p<0.001$] with a significant interaction [$F(44,396)=8.108$, $p<0.01$]. Post hoc test showed that food intake of KA group decreased on the 1st postoperative day ($p<0.01$) and increasaed on the 4th-11th days compared to controls (4th day: $p<0.01$; 5th day: $p<0.05$; 6-10th days: $p<0.01$; 11th day: $p<0.05$). Analysis of data of water intake showed significant effect of days [$F(20,360)=76.439$, $p<0.0001$], but no significant effect of treatments [$F(2,18)=3.215$, n.s.] and no significant effect of interaction [$F(40,360)=3.047$, $p<0.0001$].

4.4. Physiological challenge

The i.p. injection of 0.15 M NaCl solution resulted in similar water intake in each group of animals. One-way ANOVA showed no significant difference 4 hr [$F(2,30)=0.302$, n.s.], 6 hr [$F(3,30)=0.693$, n.s.] and 24 hr [$F(2,30)=0.549$] following the i.p. injection. After intracellular dehydration (i.p. injection of 1M NaCl) animals showed similar responses in each group. One-way ANOVA revealed that there was no significant difference 4 hr [$F(2,30)=2.811$, n.s.] and 24 hr [$F(2,30)=2.721$, n.s.] after the i.p. injection. Post hoc test showed significant increase of water intake in KA group 6 hr after intracellular dehydration (CO vs. KA, 6 hr: $p<0.05$).

4.5. General activity and stereotyped behaviors

Neurotoxic lesions of vmPFC did not produce any remarkable alteration in open field activity. One-way ANOVA revealed no significant difference among groups [$F(2,46)=1.215$, n.s.]. Analysis of stereotyped behavior showed, that there was no significant difference among groups in the number of rearing [$F(2,46)=0.834$, n.s.], grooming [$F(2,46)=0.426$, n.s.], sniffing [$F(2,46)=0.220$, n.s.], freezing [$F(2,46)=0.810$, n.s.] and bolus [$F(2,46)=1.171$, n.s.].

4.6. Taste preference investigations using two-bottle test

250 mM glucose vs. water: Preference for 250 mM glucose solution over water in each group of animals was evident. Multi-factorial repeated mesures ANOVA revealed significant effect of fluid intake [$F(1,34)=42.322$, $p<0.0001$], but no significant effect of treatments [$F(2,34)=0.816$, n.s.] or interaction [$F(2,34)=0.27$, n.s.]. Concerning only the 250 mM glucose intake, two-factorial repeated measures ANOVA analysis showed significant effect of days [$F(3,51)=4.877$, $p<0.01$) but no significant effect of treatments [$F(2,17)=0.289$, n.s.] without a significant interaction [$F(6,51)=0.568$, n.s.]. One-way ANOVA showed that there was no significant difference among the groups in the preference of 250 mM glucose [$F(2,17)=1.241$, n.s.].

500 mM glucose vs. water: Preference for 500 mM glucose solution over water was different in groups of animals. Multi-factorial repeated measures ANOVA revealed significant effect of fluid intake [$F(1,34)=194.927$, $p<0.0001$] and significant effect of treatments [$F(2,34)=5.911$, $p<0.001$] with a significant interaction [$F(2,34)=11.334$, $p<0.0001$]. Concerning only the 500 mM glucose intake, two-factorial repeated measures ANOVA analysis showed no significant effect of days [$F(3,51)=1.305$, n.s.] but significant effect of treatments [$F(2,17)=10.472$, $p<0.005$] without a significant interaction [$F(6,51)=1.404$, n.s.]. Post hoc test confirmed that 6-OHDA rats consumed significantly more 500 mM glucose solution comparing to CO, from the 2nd to the 4th day (6-OHDA vs. CO: 2nd day: $p<0.05$; 3th and 4th days: $p<0.01$), but KA lesion did not modify the consumption of 500 mM glucose solution. One-way ANOVA analysis of preference scores revealed that there was significant difference among the groups [$F(2,17)=8.691$, $p<0.01$]. Post hoc test showed that 6-OHDA-treated animals displayed significantly higher preference to the 500 mM glucose solution than CO and KA groups (6-OHDA vs. CO or KA vs. 6-OHDA: $p<0.05$, respectively).

10 mM saccharin vs. water: Multi-factorial repeated measures ANOVA revealed no significant effect of fluid intake [$F(1,34)=2.733$, n.s.], but significant effect of treatments [$F(2,34)=7.557$, $p<0.01$] with significant effect of interaction $F[2,34)=21.752$, $p<0.001$]. Concerning only the 10 mM saccharin intake, two-factorial repeated measures ANOVA analysis showed no significant effect of days [$F(3,51)=0.574$, n.s.], but a significant effect of treatments [$F(2,17)=30.083$, $p<0.001$] with significant effect of interaction [$F(6,51)=4.589$, $p<0.005$]. Post hoc tests showed that 6-OHDA animals consumed significant more saccharin compared to CO on the 1st-4th days (6-OHDA vs. CO, 1st day: $p<0.05$, 2nd-4th days $p<0.01$). One-way ANOVA analysis of preference scores revealed that there was significant difference among the groups [$F(2,17)=7.896$, $p<0.01$]. Post hoc test showed that 6-OHDA-treated animals displayed significantly higher preference to the 10 mM saccharin comapred to CO and KA animals (6-OHDA vs. CO: $p<0.01$; 6-OHDA vs KA: $p<0.05$).

500 mM glucose vs. 10 mM saccharin: Multi-factorial repeated measures ANOVA revealed significant effect of fluid intake [$F(1,34)=12.428$, $p<0.005$], but no significant effect of treatments [$F(2,34)=2.349$, n.s.] with significant effect of interaction [$F(2,34)=5.081$, $p<0.05$]. Concerning only the 500 mM glucose intake, two-factorial repeated measures ANOVA analysis showed no significant effect of days [$F(3,51)=1.424$, n.s.], but significant effect of treatments [$F(2,17)=5.187$, $p<0.05$] without a significant effect of interaction [$F(6,51)=0.263$, n.s.]. Post hoc test showed that 6-OHDA rats consumed significant more 500 mM glucose on the 3rd and 4th day compared to controls (3rd day: $p<0.05$; 4th day: $p<0.01$). One-way ANOVA analysis of preference scores revealed that there was significant difference among the groups [$F(2,17)=3.761$, $p<0.05$]. Post hoc test showed that 6-OHDA-treated animals displayed significantly higher preference to the 500 mM glucose compared to controls (6-OHDA vs. CO: $p<0.05$).

4.7. Taste reactivity test

Glucose*:* Two-way ANOVA analysis of ingestive responses revealed that there was a significant effect of concentrations [$F(3,88)=15.829$, $p<0.0001$] and a significant effect of treatments [$F(2,88)=44.544$, $p<0.0001$] without a significant interaction [$F(6,88)=2.005$, n.s.]. Post hoc tests showed that 6-OHDA group showed higher frequency of ingestive responses to 500 mM ($p<0.01$), 750 mM ($p<0.01$) and 1000 mM ($p<0.01$) glucose solutions comparing to controls. Furthermore, KA group showed significantly more ingestive responses to 750 mM glucose solution compared to controls. Glucose elicited relatively few rejective responses in

each concentration in each group. Two-way ANOVA analysis of rejective respones revealed that there was no significant effect of concentrations [$F(3,88)=0.868$, n.s.] but a significant effect of treatments [$F(2,88)=7.930$, $p<0.01$] without a significant interaction [$F(6,88)=0.746$, n.s.]. Post hoc test revealed that KA-treated animals showed ewer rejective responses to 750 mM glucose solution compared to controls (KA vs. CO: $p<0.05$).

Saccharin: Two-way ANOVA analysis of ingestive responses showed that there was a significant effect of concentrations ($F[3,88]=9.133$, $p<0.0001$) and treatments ($F[2,88]=15.604$, $p<0.0001$) with significant interaction ($F[6,88]=5.524$, $p<0.0001$). Post hoc tests revealed that KA and 6-OHDA rats showed more ingestive responses to 100 mM (CO vs. KA: $p<0.01$; CO vs. 6-OHDA: $p<0.01$) and to 1000 mM saccharin solution (CO vs. KA: $p<0.01$; CO vs. 6-OHDA: $p<0.01$) than controls. The most liked concentration was 1 mM saccharin in CO group, but 100 mM and 1000 mM saccharin was the most preferable solution in lesioned (KA vagy 6-OHDA) groups. Saccharin elicited relatively few rejective responses in each concentration in each group. Two-way ANOVA analysis of rejective respones revealed that there was no significant effect of concentrations ($F[3,88]=1.557$, n.s.) but a significant effect of treatments ($F[2,88]=6.143$, $p<0.01$), without a significant interaction ($F[6,88]=0.934$, n.s.). Post hoc test revealed that 6-OHDA-treated animals showed significant fewer rejective responses to the 1000 mM saccharine solution compared to CO rats ($p<0.01$).

NaCl: According to the statistical analysis of ingestive responses, there was a significant effect of concentrations ($F[2,88]=17.227$, $p<0.0001$) and treatments ($F[2,88]=17.227$, $p<0.0001$) without significant interaction ($F[6,88]=1.334$, n.s.). Post hoc tests revealed that KA rats showed more ingestive responses to 1000 mM (CO vs. KA: $p<0.01$) and 1500 mM (CO vs. KA: $p<0.05$) NaCl solutions compared to CO rats. NaCl elicited relatively few rejective responses in each concentration in each group. Two-way ANOVA analysis of rejective respones revealed significant effect of concentrations ($F[3,88]=9.995$, $p<0.0001$) and significant effect of treatments ($F[2,88]=15.155$, $p<0.0001$) with significant interaction ($F[6,88]=8.559$, $p<0.0001$). Post hoc test revealed that KA and 6-OHDA-treated animals showed fewer rejective responses to the 1500 mM NaCl solution compared to CO rats (CO vs. KA: $p<0.01$; CO vs. 6-OHDA: $p<0.01$).

Citrate: On the basis of two-way ANOVA analysis of ingestive responses, there was a significant effect of concentrations ($F[3,88]=3.841$, $p<0.05$), and treatments ($F[2,88]=21.117$, $p<0.001$) without significant interaction ($F[6,88]=1.161$, n.s.). Post hoc tests revealed that 6-

OHDA group showed less ingestive responses to 1 mM, a 10 mM and a 100 mM citrate solutions compared to controls (CO vs. 6-OHDA: 1 mM: $p<0.05$, 10 mM: $p<0.01$, 100 mM: $p<0.05$). Two-way ANOVA analysis of rejective respones showed significant effect of concentrations ($F[3,88]=3.752$, $p<0.05$), and significant effect of treatments ($F[2,88]=4.628$, $p<0.05$) without a significant interaction ($F[6,88]=2.054$, n.s.). Post hoc test showed that KA-treated animals showed more rejective responses to 100 mM citrate solution compared to CO and 6-OHDA rats (KA vs. CO: $p<0.05$; KA vs. 6-OHDA: $p<0.005$).

Quinine: Quinine elicited relatively few ingestive responses in each concentration in each group. Two-way ANOVA displayed that there was a significant effect of concentrations [$F(3,88)=24.079$, $p<0.001$] and a significant effect of treatments [$F(2,88)=7.143$, $p<0.01$] without a significant interaction [$F(6,88)=1.927$, n.s.]. Post hoc test showed that 6-OHDA treated animals displayed less ingestive responses to 0.125 mM quinine solution than COgroup (6-OHDA vs. CO: $p<0.01$). Two-way ANOVA analysis of rejective responses revealed that there was a significant effect of concentrations [$F(3,88)=6.202$, $p<0.01$] and a significant effect of treatments [$F(2,88)=29.058$, $p<0.001$] without a significant interaction [$F(6,88)=0.985$, n.s.]. Post hoc test showed, that KA-treated animals displayed significantly more rejectivity to the two higher concentrations of quinine solutions than controls (KA vs. CO at 1.25 mM: $p<0.05$ and at 2.5 mM: $p<0.01$).

4.8. Conditioned Tase Aversion (CTA)

4.8.1. Acquisition of CTA

Saccharin: When 10 mM saccharin solution was used as CS, two-way ANOVA revealed that there was no significant effect of treatments ($F[2,34]=2.106$, n.s.) but there was a significant effect of trials ($F[1,34]=8.622$, $p<0.05$) along with a significant interaction of treatments and trials ($F[2,34]=8.549$, $p<0.005$). Post hoc test displayed that well defined avoidance developed in control group to saccharin solution because their fluid intake significantly decreased on Acquisition day compared to Conditioning day ($p<0.01$). Contrarily, vmPFC lesioned animals (kainate or 6-OHDA groups) did not display avoidance to saccharin solution because they consumed almost as much of the discomfort associated tastant on the Acquisition day as they did on the Conditioning day.

NaCl: When 50m M NaCl solution was used as CS in the CTA paradigm, two-way ANOVA revealed that there was no significant effect of treatments ($F[2,38]=0.535$, n.s.) but there was

a significant effect of trials ($F[1,38]=4.381$, $p<0.05$) without a significant interaction of treatments and trials ($F[2,38]=0.715$, n.s.). Post hoc test showed that controls consumed significantly less amount from the NaCl-solution during Acquisition, than in Conditioning ($p<0.05$). That is, in control group significant avoidance developed in contrast to both (kainate or 6-OHDA) lesioned groups, where no significant difference could be recorded between the intakes of Conditioning and Acquisition.

Citrate: Two-way ANOVA analysis of CTA to 10 mM citrate revealed that there was a significant effect of treatments ($F[2,36]=12.912$, $p<0.0001$), a significant effect of trials ($F[1,36]=6.91$, $p<0.05$) along with a significant interaction of treatments and trials ($F[2,36]=4.464$, $p<0.05$). Post hoc test showed that a well-defined avoidance developed in control animals to citrate solution because their fluid intake significantly decreased on Acquisition day compared to Conditioning day ($p<0.005$). Contrarily, the vmPFC lesioned animals (in the kainate or 6-OHDA groups as well) consumed almost as much as the discomfort associated tastant on Acquisition day as they did on the Conditioning day. Furthermore, post hoc test showed that citrate intakes of lesioned animals (kainate or 6-OHDA groups) measured on the Acquisition day were significantly higher than the corresponding value of the controls (Control vs. Kainate: $p<0.005$; Control vs. 6-OHDA: $p<0.005$).

Quinine: Two-way ANOVA analysis of CTA to 0.25 mM quinine revealed that there was no significant effect of treatments ($F[2,40]=2.031$, n.s.), a significant effect of trials ($F[1,40]=120.1$, $p<0.0001$) without a significant interaction of treatments and trials ($F[2,40]=0.205$, n.s). Post hoc analysis showed a robust avoidance to quinine on the Acquisition day in each group of animals (Conditioning vs. Acquisition in Control, Kainate, 6-OHDA: $p<0.001$, respectively).

4.8.2. Retrieval of CTA

Saccharin: When 10 mM saccharin solution was used as CS, two-way ANOVA revealed that there was a significant effect of treatments ($F[2,45]=4.691$, $p<0.05$), a significant effect of trials ($F[2,45]=79.897$, $p<0.001$) along with a significant interaction of treatments and trials ($F[4,45]=2.706$, $p<0.05$). Post hoc test showed that after the development of CTA control animals showed a retained avoidance because their saccharin intake in Retrieval remained significantly lower compared to that on Conditioning day ($p<0.01$). Contrarily, the consumptions of lesioned groups (kainate or 6-OHDA groups) in Retrieval did not differ

significantly from that measured on the Conditioning day and, moreover, it was significantly higher than that measured on Acquisition day (Retrieval vs. Acquisition, Kainate: $p<0.001$; 6-OHDA: $p<0.001$) showing lack of retrieval. Additionally, post hoc test showed significant difference among groups in Retrieval ($p<0.01$). Lesioned animals drank significantly more saccharin during Retrieval compared to controls (Control vs. Kainate: $p<0.01$; Control vs. 6-OHDA: $p<0.01$).

NaCl: Two-way ANOVA revealed that there was no significant effect of treatments ($F[2,51]=1.945$, n.s) but there was a significant effect of trials ($F[2,51]=16.911$, $p<0.001$) without a significant interaction of treatments and trials ($F[4,51]=2.351$, n.s.). Post hoc test showed that control rats displayed a retained avoidance, because their consumption in Retrieval was significantly lower than that measured in Conditioning ($p<0.05$). Contrarily, in lesioned groups (kainate or 6-OHDA groups) there was no significant difference in intake between this two trials, but their consumptions were significantly higher in Retrieval compared to that in Acquisition (Retrieval vs. Acquisition, Kainate: $p<0.01$; 6-OHDA: $p<0.01$), which means that lesions impaired the retrieval of CTA.

Citrate: When 10 mM citrate was the CS in the CTA paradigm all groups of animals showed a retained avoidance in Retrieval. Two-way ANOVA revealed that there was no significant effect of treatments ($F[2,57]=0.611$, n.s.), but there was a significant effect of trials ($F[2,57]=30.764$, $p<0.0001$) without a significant interaction of treatments and trials ($F[4,57]=0.195$, n.s.). Post hoc test showed significant difference between the consumptions in Retrieval and Conditioning (Retrieval vs. Conditioning in Control, Kainate, 6-OHDA: $p<0.01$, respectively), which means that each group displayed retained avoidance.

Quinine: Lesions of vmPFC did not modify the retrieval of a previously learned taste avoidance if the CS was 0.25 mM quinine. Two-way ANOVA revealed that there was no significant effect of treatments ($F[2,54]=0.147$, n.s.) but there was a significant effect of trials ($F[2,54]=90.837$, $p<0.001$) without a significant interaction of treatments and trials ($F[4,54]=0.366$, n.s.). Post hoc test showed significant difference between the consumptions in Retrieval and Conditioning in each group of animals (Retrieval vs. Conditioning in Control, Kainate, 6-OHDA: $p<0.001$, respectively), which indicate that each group displayed retained avoidance.

4.9. Investigation of „hedonic shift" after CTA

Before the development of CTA, each group of animals showed similarly more ingestive and less rejective responses to 10 mM saccharin. One-way ANOVA revealed that there was no significant different in the number of ingestive ($F[2,17]=0.269$, n.s) and rejective ($F[2,17]=1.041$, n.s.) responses among groups. But, after acquisition of CTA, one-way ANOVA showed significant difference among groups ($F[2,17]=6.697$, $p<0.01$). Post hoc test revealed that the number of ingestive respones after CTA was significant less in CO rats compared to KA and 6-OHDA animals (KA vs. CO: $p<0.01$; 6-OHDA vs. CO: $p<0.005$). Two-way analysis of data of hedonic evaluation revealed that there was significant effect of trials ($F[1,34]=95.328$, $p<0.0001$) and significant effect of treatments ($F[2,34]=45.653$, $p<0.0001$) with significant effect of interaction ($F[2,34]=46.435$, $p<0.0001$). Post hoc test showed significant difference between the CO and lesioned groups: the taste solution was more palatable for KA group and 6-OHDA animals compared to controls (KA vs. CO: $p<0.001$; 6-OHDA vs. CO: $p<0.001$). Moreover, saccharine solution was more unpalatable for CO rats in the Acquisition than on the Conditioning day compared to controls (CO: Conitioning vs. Acquisition: $p<0.0001$).

5. DISCUSSION

Body weight, food and fluid intake

The data of our present experiments showed that bilateral kainate lesion of the vmPFC did not cause serious deficit in body weight, food and water intake. The transient weight loss observed in KA goup lasted for one week after surgery. The dynamics of body weight changes are concerned there are contradictory results in the literature. Namely, it was reported that after ablation of the whole mPFC animals achieved their preoperative body weight c.a. within 20 (18-31) days after the operation [32]. We suppose that the distinct results is due to the different size of lesions. The destruction of vmPFC neurons altered food intake as well. Hypophagia developed on the 1st day after operation and it was followed by a mild hyperphagic phase lasting for 8 days. The tendency of increased food intake was observed also in the 2nd week after the lesion. We hypothesize that hypophagia may be due to a compensatory mechanism for weight loss. Our data indicate that vmPFC neurons do not play a role in the regulation of water balance, since the lesion did not alter the water intake. **In our experiments, catecholaminergic lesion of vmPFC did not cause any changes in body**

weight, food or fluid intake. A similar result was obtained in our previous experiments, where iontophoretic 6-OHDA lesion of dmPFC did not result in deficit in weight, food and fluid intake [26]. Contrarily, microinjection of 6-OHDA into the vmPFC or dmPFC resulted in sustained weight loss [29, 33]. The microiontophoretic technique developed and routinly used in our laboratory create distinct, small neurochemical lesions in the vmPFC and thereby the side effects resulting in behavioral alterations caused by large lesions, could be avoided [21, 22].

Physiological challenges

Bilateral kainate or 6-OHDA lesion of the vmPFC did not result in any change in adaptation mechanism to physiological challenges. The procedure revealed similar increase of water intake in all three groups following i.p. injection of NaCl solutions. These results are consistent with our earlier data and previous reports of others [27, 34, 35], where dmPFC or whole mPFC lesioned animals were also capable to adapt either water deprivation or intracellular dehydration. **Based on our data and these findings we can summarize that neurons and catecholaminergic terminals in vmPFC do not play direct role in the formation of response to physiological challenge.**

General activity and stereotyped behaviors

Kainate or 6-OHDA lesion of the vmPFC did not alter the general activity and stereotyp behavior in open field test. Our results are consistent with many of the studies which reported that mPFC lesion did not modify spontaneous locomotor activity. Namely, aspiration, NMDA or ibotenic acid lesion of the whole mPFC does not produce any change in the locomotor activity [36-38]. Furthermore, it has been shown that microinjection of ibotenic acid or 6-OHDA into the prelimbic and infralimbic areas of the mPFC does not influence spontaneous locomotor activity [39, 40]. Microiontophoretical application of kainate or 6-OHDA into the dmPFC produced enhanced activity in exploratory, orientation and foraging behavior (tested as rearing, sniffing and grooming) and vertical activity (crossing) [26]. Furthermore, injection of 6-OHDA into the dorsal area of the PFC increased locomotor activity [29]. **According to our results, the vmPFC is not involved in the control of open field activity and stereotype behavior.**

Taste Preference

Neuron lesion in vmPFC did not alter the consumption and preference of 250 mM glucose, 500 mM glucose and 10 mM saccharin solutions in two-bottle preference test. **After catecholaminergic lesion of vmPFC, rats showed normal preference to 250 mM glucose, but an increased preference to 500 mM glucose and 10 mM saccharin solutions over water. 6-OHDA lesioned animals displayed elevated preference to 500 mM glucose over 10 mM saccahrine. In preference test between two sweet solutions with different energy content, 6-OHDA group preferred 500mM glucose over 10 mM saccharin, while control animals showed similar preference to the two sweet flavored solutions.** Interestingly, selective destruction of only dopaminergic terminals in dmPFC elevated the preference to both 250 mM and 500 mM glucose solutions [33]. The difference in results may derive from the anatomical, neurochemical and functional differences between dmPFC and vmPFC areas [1] or from distinct dopamine and noradrenaline innervation and receptor density [31]. **On the basis of our data we can suppose that particularly the catecholaminergic innervation of vmPFC is involved in the control of consumption of highly palatable foods. Loss of these fibers can lead to elevated preference and hedonic feeding.**

Taste reactivity

The lesion of vmPFC neurons resulted in increased hedonic value mainly in the case of higher concentrations of pleasant (sweet and salty) taste solutions. In the case of unpleasant tastes (citrate, quinine), KA lesion shifted the hedonic value in negative direction, since it incresed the number of rejection responses. As a result of the lesion, animals evaluated the pleasant taste solutions to be even more pleasant and the unpleasant tastants even more unpleasant. **Our results showed that catecholaminergic afferents of the vmPFC also influence the hedonic evaluation of taste stimuli. Damage of these terminals resulted in increased hedonic responses to pleasant tastants and decreased hedonic evaluation of unpleasant taste solutions.** These data suggest, that lack of catecholaminergic axon-terminals in vmPFC provokes increased sensitivity and „finickiness" – like behavior to aversive tastants. Our results are consistent with the data of earlier studies in the literature, which described that rats drank less amount from the quinine adulterated solution after lesion of the mPFC [34]. According to our results we can declare, that „finickiness" provoked by lesion of the vmPFC, is a consequence of an elevated hedonic sensitivity towards aversive

taste stimuli. This phenomenon is mediated specifically by catecholaminergic neurotransmission within the vmPFC of rats. **Our data suggest, that neuron and catecholaminergic innervation of vmPFC are involved in the hedonic evaluation of palatable and aversive tastants and plays critical role in the control of consumption of highly palatable and less- or unpalatable foods.**

Conditioned taste aversion

The present experiments demonstrated that kainate or 6-OHDA lesion of the vmPFC resulted in deficit in acquisition of CTA to 50 mM NaCl, 10 mM saccharin and 10 M citrate solutions, but did have no effect to 0.25 mM quinine tastant. Neuron or katecholaminergic lesion of vmPFC attenuated the retrieval of CTA to 50 mM NaCl and 10 mM saccharin, but not to 10 mM citrate and 0.25 mM quinine. Our data show, that vmPFC are involved in the acquisition of CTA only for stongly and weakly palatable taste stimuli and in retrieval of CTA only for stongly palatable tastants.

CTA learning deficit specific to palatable tastants has also been demonstrated in mice lacking D1 DA receptors [41]. These animals were able to acquire and express a CTA to moderate concentration of NaCl, but did not express an appropriate CTA to a sweet taste paired with LiCl. Similar result was described in another study, where injection of GABA receptor antagonist into the ventral pallidum produced deficit in CTA to saccharin but had no effect to quinine CTA [42]. It has been confirmed that the mPFC is sensitive to highly palatable tastes, since palatable tastants stimulate dopaminergic transmission in the mPFC [43]. It has been demostrated that catecholaminergic terminals respond differently, namely reciprocally to tastes with different hedonic values in subcortical brain regions. A number of pharmacological studies support the critical role of dopamine and noradrenaline in distinct phases of aversive learning and memory processes. It has been demonstrated that dopamine in vmPFC plays important role in the acquisition and expression of conditioned fear [44] and in the persistent storage of different types of aversive learning [45]. Dopamine is involved also in the formation of short-term memory trace related to gustatory CS in CTA which has been confirmed in other brain regions, such as NAc shell [12] and lateral hypothalamus [13]. Several studies can be found in the literature, which report on the role of noradrenergic system in aversive learning and in the retrieval of these memories as well [46]. Data in the literature confirmed the crucial role of noradrenergic system in CTA in different brain areas, such as locus coeruleus and basolateral amygdala [14, 47, 48]. It has been also demonstrated

that blocking the noradrenergic mechanism in vmPFC impaired both acquisition and retrieval of CTA, but does not influence non-aversive learning processes and taste perception [49].

The results presented here show that both kainate or 6-OHDA lesions similarly affected CTA. **The similar results observed in lack of catecholamine innervation or local neurons in vmPFC show that both neural elements are necessary for CTA acquisition and retrieval processes to palatable tastants. On the basis of the present work, we assume that the local neurons and catecholaminergic nerve terminals of vmPFC play an important role in learning and long-term storage (retrieval) particularly for the strongly palatable tastes and partially for weakly palatable tastant in CTA.**

„Hedonic shift" after CTA

Lesion of neurons or catecholaminergic terminals in vmPFC did not alter the hedonic evaluation of 10 mM saccharin prior the acquisition of CTA. Contrarily, after CTA increased the number of ingestive responses in both lesioned groups compared to CO group. **The hedonic scale represents that control animals evaluated 10 mM saccharin solution unpalatable, but vmPFC lesioned groups found it pleasant. Our results confirmed our hypothesis that the lesions of vmPFC affect not only conditioned taste aviodance and hedonic perception of tastes, but also the hedonic shift, namely the expression of conditioned disgust.**

6. SUMMARY

A) Ionophoretic microlesion of vmPFC neurons:

1) resulted in temporary body weight loss

2) initial hypophagia was followed by transient hyperphagia

3) did not change ad libitum water intake

4) did not affect the adaptive mechanisms after physiological challenges

5) did not change the general activity and stereotyped behaviors

6) did not influence the preference for sweet solutions

7) caused enhanced hedonic value of medium high concentration of glucose, high concentration of saccharin and NaCl solutions. In the case of very unpleasant, high concentrations of taste stimuli the lesion increased the number of aversive reactions, which may indicate hyperreactivity

8) loss of neurons prevented the associative phase of taste aversion learning to medium and high palatable taste stimuli

9) induced impaired retrieval of a previous learned aversive taste information in case of high palatable taste stimuli

10) resulted in deficit of "hedonic shift" in conditional taste aversion learning mechanism

B) Ionophoretic 6-OHDA microlesion of catecholaminergic terminals in vmPFC:

1) did not change the body weight

2) did not affect food intake

3) did not cause change in water intake

4) did not affect the adaptive mechanisms after physiological challenges

5) did not change the general activity and stereotyped behaviors

6) caused increased preference of high concentration of sweet solutions irrespective of their energy content, but the lesion did not influence the preference of low concentration of glucose solution

7) loss of catecholaminergic innervation enhanced the hedonic value of high concentrations of glucose, saccharin and NaCl solutions. In the case of unpleasant taste stimuli, the lesion decreased the number of aversive responses. The lesion provokes increased sensitivity and „finickiness" – like behavior to the lowest concentration of quinine.

8) prevented the taste aversion learning to moderate and high palatable taste stimuli

9) resulted impaired retrieval of previous lerned aversive taste information in case of high palatable taste stimuli

10) attenuated the "hedonic shift" in conditional taste aversion learning mechanism

We can conclude that intrinsic neurons and catecholaminergic inputs of vmPFC are essential in regulation of consumption of high palatable foods and in avoidance of unpleasant tastes. Dysfunction of the vmPFC can lead to overeating and obesity.

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8. LIST OF PUBLICATIONS

A) Publications related to the thesis

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