Maternal behavior and stress-reactivity in the vasopressin-deficient Brattleboro rats

Doctoral Theses

dr. Anna Fodor

Semmelweis University
János Szentágothai School of Neurosciences

Supervisor: Dr. Dóra Zelena, Ph.D., senior research fellow

Official referees: Dr. Árpád Dobolyi, Ph.D., senior research fellow
Dr. György Lévay, Ph.D., scientific advisor

Chairman of committee of comps: Dr. Erzsébet Ligeti, member of the Hungarian Academy of Sciences, professor
Members of committee of comps: Dr. Pál Riba, Ph.D., associate professor
Dr. István Gacsályi, Ph.D, researcher

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INTRODUCTION

The mother-infant relationship is an important factor in the development of offspring and there are broad individual differences in mother styles that could affect emotionality and stress reactivity of offspring at adulthood. General psychological condition of the mother (e.g. mood, anxiety and stress level) could affect the normal mother-infant interaction. Postpartum depression (PPD) is a serious medical condition that affects approximately 10% to 20% of mothers during the first 4 weeks after delivery. Symptoms of PPD can include labile mood with prominent anxiety and irritability. In humans, children of depressed mothers tend to show abnormal cognitive, motor and social development and are more likely to experience depression or anxiety later in life. Despite its clinical importance this disease is underdiagnosed and undertreated. Maternal adaptation, such as decreased anxiety and attenuated stress responsiveness, are necessary to enable successful postnatal development of the offspring. Chronic stress in pregnancy is a known risk factor for postpartum mood and anxiety disorders. Stress is the body's reaction to a challenge that requires a physical, mental or emotional adjustment or response. Selye was the first to suggest that neuroendocrine factors play a decisive role, and he considered the activation of the hypothalamo-pituitary-adrenocortical (HPA) axis (so called stress-axis) is one of the main background mechanism of adaptation.

Arginine-vasopressin (AVP) is a peptide hormone produced mainly in the magnocellular cells of hypothalamus. The brain contains several populations of smaller, AVP synthesizing parvocellular neurons located within the paraventricular (PVN) and suprachiasmatic (SCN) nuclei of the hypothalamus, medial amygdala (MeA) and the bed nucleus of the stria terminalis (BNST). The medial part of the parvocellular PVN (mpPVN) contains corticotropin-releasing hormone (CRH) producing neurons in colocalization with AVP projecting to the median eminence as part of the HPA-axis. The primary physiological function of AVP is to stimulate water retention by increasing the water permeability of the distal tubules of the kidneys. AVP has an important role in affiliative behaviors in all vertebrates, too. The female brain AVP system becomes activated around parturition and during lactation. AVP levels peak on the day before parturition in PVN. Therefore an involvement of AVP in the behavior of lactating mothers can be supposed. Patients with major depression have significantly elevated

plasma AVP compared to healthy controls. Depressed patients with the melancholic subtype have significantly greater AVP mRNA in the PVN.

Maternal behaviors in rodents include a number of subcomponents, such as nest building, pup retrieval, nursing, licking and grooming of pups, and maternal defense of the nest against potential intruders (maternal aggression). In the nest the mother crouches over the young to nurse them and to keep them warm. They lick the anogenital area of their young, stimulate reflexive urination, and ingest the urine. This behavior serves to stimulate pups, modify body and brain temperature, and allows the dam to reclaim salt and water to meet the physiological demands of lactation. Moreover, the frequency of licking-grooming can effect changes in the genetic information of the pups, which generate long-term consequence (e.g. different hippocampal glucocorticoid receptor expression). Maternal aggression is highly expressed during lactation and serves to protect the developing young from intruders that may injure the offspring.

Nulliparous or virgin females do not show maternal behavior. The onset of maternal behavior is hormonally determined, but it appears to have a nonhormonal basis, too. A dominant player of the control of the appetitive aspects of maternal behavior in rats and other species is the medial preoptic area (mPOA) in the rostral hypothalamus and the adjoining ventral bed nucleus of the stria terminalis (vBNST).

During lactation, female rats undergo numerous neuromorphological, neuroendocrine, metabolic, and behavioral changes, which favor beneficial interactions with the offspring. An increased resting activity of the HPA axis can be measured during pregnancy and lactation, suggesting that these reproductive states lead to chronic load in females. The modifications of the HPA axis include an increase in CRH and AVP mRNA levels in the PVN neurons and elevated plasma ACTH and corticosterone levels. Interestingly, when exposed to defined stressors, lactating rats exhibit – compared with virgin females – reduced ACTH, corticosterone responses. In the PVN of lactating rats, CRH mRNA levels fail to increase in response to a defined stressor exposure, in contrast to both AVP mRNA levels and the number of neurons exhibiting the co-localization of AVP and CRH. During lactation, the ACTH response to CRH is blunted, whereas AVP triggers an increased ACTH release. This suggests a shift in the sensitivity of the pituitary corticotrophs from CRH to AVP in response to additional stressors. This hypothesis would fit the observation that maternal adaptations, such as

decreased anxiety and attenuated stress responsiveness, are necessary to enable the successful postnatal development of the offspring, and a shift from a CRH- to an AVP-stimulating ACTH release could be one of the most important components of this adaptation.

AIMS

Given all the above, we aimed to clarify if the congenital lack of vasopressin (AVP) influences

(1) maternal behavior (undisturbed maternal and separation-induced pup retrieval behavior and the influence of peripheral administration of a V2 receptor agonist on this behavior)

(2) the development of a depressive-, and anxiety-like phenotype, changes in maternal aggression and impulsivity

(3) the basal and stress induced activity of the HPA axis during lactation (compared with virgin animals)

(4) the basal and stress induced c-Fos activation in the PVN, amygdala, mPOA and BNST.

Our results may give further details to the role of AVP in the behavior of the mothers (both maternal care and development of PPD) and its underlying brain areas without the need of further manipulations which could be very important in the case of undisturbed maternal care.

MATERIAL AND METHODS

The Brattleboro homozygous rat (AVP-) has a spontaneous mutation in the AVP precursor and – as a consequence – AVP is not synthesized, leading to a diabetes insipidus phenotype. This strain is a good model for studying the role of AVP in physiological and psychological processes without the need of further manipulations (i.e. injections and operations). AVP-deficient and control Brattleboro rats came from a colony maintained in our Institute. Female subjects were mated with males of different homozygous genotype, i.e. AVP-deficient females mated with control males, while control females mated with AVP-deficient males. With this design the genotype of all

pups was heterozygous; therefore, litter genotype did not differ between subjects and it could not alter maternal behavior. After delivery litters were culled to 3 males and 3 females to control for the behavioral effects of quantity and quality of pups. Animals were kept on a light/dark cycle of 12 h. The temperature and humidity were kept at 23 ± 2 °C and 60 ± 10%, respectively. All experiments were conducted in accordance with the European Union Directive of 2010 (2010/63/EU) and were reviewed and approved by the Animal Welfare Committee of the Institute of Experimental Medicine, Budapest, Hungary.

Maternal behavior

To exclude the possible influence of diabetes insipidus on maternal behavior half of the AVP- dams were implanted subcutaneously with an osmotic minipump containing desmopressin (DDAVP, V_2 receptor agonist) on the day of delivery under ether anesthesia (approximately 3 min intervention). Further AVP- and AVP+ mothers underwent sham operation.

- Undisturbed maternal behavior

The undisturbed maternal behavior was observed during three 60 min daily observation periods, for the first 7 postnatal days. Observations were performed at two periods during the light phase (8:30 and 14:30 h, lights ON at 7:00 h) and at one period during the dark phase (20:30 h, lights OFF at 19:00 h). Within each observation period, the behavior of each mother was scored 20 times spaced 3 min each one (20 observations×3 periods per day×7 days=420 observations/mother). During the experiment the following behaviors were scored as present or absent: (1) LG: mother licking–grooming any pup (body+anogenital region), (2) mother nursing pups in an arched-back posture with rigid limbs (“high kyphosis”), (3) mother nursing in a “blanket” posture in which the mother just lies over the pups (“prone nursing”), but did not have her back arched and there was no obvious extension of her legs, (4) mother nursing in a “passive” posture (“supine nursing”) in which the mother lies on her back or side while the pups are nursed, (5) mother out of the nest (mother drinking (as AVP- rats supposed to drink more and the administration of DDAVP should normalize this behavior, we used this parameter for validation of our method) or eating).

- Pup retrieval test (PR)

During the second experimental series, on postnatal day 8, all pups were separated from their mothers into a new cage for 5 min. After this brief separation, the entire litter was returned to their mothers into the maternity cage and the pups were spread all around the cage. The mother was then observed for 10 min to measure: (1) latency to carry the first pup, (2) latency to return the first pup into the nest, and (3) latency to return all pups into the nest.

Psychological condition of the mother

- Anxiety- and depression-like behavior:

Elevated Plus Maze (EPM)

To measure anxiety, dams were exposed to the EPM once between postnatal days 10-15 during the morning hours. The duration of the test was 5 min. Rats were introduced in the center of the maze facing a closed arm. Animal behavior was videotaped by a camera positioned above the maze and analyzed later. Percentage of time spent in open arms and percentage of open arm entries (number of open arm entries/number of open plus closed arm entries) were calculated and used as measures of anxiety (entry: at least three paws in an arm). Closed arm entries were considered as indicators of general locomotor activity.

Anhedonia test - Sweet preference

Once between postnatal days 12–17 dam's sucrose preference versus a solution containing ethanol was measured using a two-bottle, free-choice test (24 h/day). The first bottle contained 2.5 w/v sucrose diluted in tap water and the second bottle contained 8% ethanol v/v in 2.5 w/v sucrose. Sucrose was added to the alcohol to make the solution more palatable to the rat and increase consumption. Fluid consumption was measured by subtracting the final weight of the bottle from the initial weight. The percentage of sucrose solution from the total liquid ingested (sucrose preference) was measured. To confirm the outcome in a separate set of animals a saccharin consumption test was conducted. We have chosen this palatable solution because it has no caloric value. For two days the animals were allowed free access to two

bottles of tap water, to acclimatize the animals to the system. Then we measured 0.1 w/v saccharin versus water intake for 24 h and the saccharin preference was calculated.

Forced Swim Test (FST)

The FST is a widely used pharmacological model for assessing antidepressant activity and active/passive behavior in front of stressful situations. Once between postnatal days 15–20 dams were individually placed in a glass cylindrical tank and they were forced to swim for a 15 min. period. The swimming session was videotaped by a camera positioned in front of the water tanks and subjected to analyze later on. The following measures were taken: (1) floating (immobility), when their general activity was minimized to occasional and small movements of legs or tail necessary to keep their heads above the water; (2) struggling (climbing), a vertical intense movement of paws, when animal permanently breaks the water surface; (3) swimming, when animals were making mild swimming movements, more than those necessary to merely keep the head above water and (4) diving. After the swimming sessions, the rats were removed from the tank, carefully dried by paper towels and returned to their home cages. Water in tank was changed after each animal.

- <u>Maternal aggression test - resident-intruder test</u>

Lactating female rats were faced with a male Wistar opponent in their home-cage on lactation days 5 or 6 and 18 or19. The encounter lasted 10 min because of the severity of the maternal attacks. Behavior was video recorded and scored later by an experimenter blind to treatment conditions. Behavior analysis focused on the consummatory phase of aggressive behavior i.e. on biting attacks. In addition to quantitative measures (e.g. attack counts and latency), qualitative measures (attack type and context) were also recorded. Attack episodes were analyzed in detail at low speed (frame-by-frame when necessary) for identifying the type of attacks. Hard and soft, vulnerable and non-vulnerable, as well socially signaled and non-signaled attacks were differentiated. An attack was identified as hard bite when it involved kicking (clinch fights) or induced a strong startle response in the intruder (jumps or immediate submission). Soft

bites were not associated with kicking and induced no response or mild quivering only. An attack was considered a vulnerable area-attack if it targeted the head (areas anterior to the ears), throat (the ventral area below the ears), belly (ventral areas between legs), or the paws of the opponent. The back and the flanks (posterior to the ears and dorsal to the legs) were considered non-vulnerable targets. An attack was considered signaled if it was delivered within an aggressive context (i.e. it was preceded by aggressive grooming, lateral threat, chasing, wrestling, offensive upright, and dominant posture), and it was considered non-signaled if it was performed within a non-aggressive context (e.g. it was preceded by exploration, self-grooming or social investigation). Behavior was video-recorded for 20 min after the termination of the encounter, during which the spontaneous maternal behavior of dams was recorded (time spent with nursing, licking-grooming the pups and anxiety-like behaviors).

- Impulsivity - delay discounting apparatus:

Experiments assessing impulsive behavior were conducted using automated operant chambers equipped with two nose-poke holes with infrared sensors and LED lights, a chamber light and a feeder device with a magazine into which food pellets were dropped. Chambers were placed inside sound-attenuated wooden cubicles and were controlled via computers running Med-PC IV software. During the *training phase*, animals were placed inside a chamber for 30 min daily for 5 days. A response on one of the nose-poke holes was rewarded with one 45 mg food pellet (small reward), while a response on the other hole resulted in five 45 mg food pellets (large reward). Both types of reward were presented immediately after the response and were followed by a 25 s timeout with the chamber light switched on. During the timeout period, responses were not rewarded but were registered. Animals were placed in the same chamber with the same nose-poke hole side assignment throughout the experiment. At the end of the training phase, the animals were expected to respond on the nose-poke hole that was paired with the large reward in approximately 90% of all trials. During the *test phase*, each animal was placed in a chamber for 30 min daily for 8 days. The procedure was similar to that described for the training phase, but a delay was inserted before the large reward. The delay was fixed for

each daily session and was increased progressively over subsequent days (10, 20, 30, 45, 60, 80, 100 and 120 s). Responses during these delays were not rewarded, but they were recorded by the software. Sessions of the test phase were conducted at the same time as sessions of the training phase. During the test phase, subjects were expected to shift their preference from the nose-poke hole rewarded by the delayed large reward to the nose-poke hole rewarded by the immediate small reward. During the training sessions, we recorded the preference of the nose-poke hole paired with the large reward (large reward preference) to assess learning capabilities. Increases of greater magnitude in large reward preference indicated quicker learning. During the test phase, large reward preferences were indicative of non-impulsive choices. This variable is negatively associated with choice impulsivity, which refers to an inability to prefer a larger, delayed reward over an immediate smaller one. The number of inadequate responses (the sum of responses during timeouts and delays), which reflects the number of premature, impulsive responses, was also evaluated. With this measure, we were able to assess motor impulsivity, which is defined as the inability to inhibit inappropriate actions. In the third phase the benzodiazepine, chlordiazepoxide (CDP), and the tryciclic antidepressant, imipramine (IMI), were dissolved in saline. These drugs were administered intraperitoneally 15 min (CDP) or 60 min (IMI) before the start of the experiment at a dose of 0 (vehicle) or 10 mg/kg in a volume of 1 ml/kg.

Stress-axis:

- Basal comparison of virgin and lactating, control and AVP-deficient females:

After measuring of the somatic parameters (bodyweight, adrenal mass) the rats were decapitated under basal conditions at the end of the lactation period (the trunk blood was collected); the brain and hypophysis were rapidly removed from the skull. After successful hybridization, CRH (brain) and proopiomelanocortin (POMC, ACTH precursor; hypophysis) mRNA levels were quantified. The average grayness density of 3 sections on both hemispheres (CRH) or 6 sections (POMC) taken at 80 μm intervals was used for analysis.

- Stress-reactivity:

The time course of the hormone levels was established by repeated blood sampling using an iv. catheter implanted into the right jugular vein under anesthesia. After collection of the first sample, the rats were exposed to defined stimuli, and blood samples (0.4 ml/sample) were collected at defined time points without additional animal handling with a connected long piece of polyethylene tubing. (1) Egg white injection: Fresh, filtered egg white was slowly injected through the jugular catheter at a dose of 1 ml/kg. Blood samples were collected immediately before (at 0 min) and 15, 30, 60, 90, and 120 min after injection. (2) Insulin injection: After 18 h of fasting, hypoglycemia was induced by ip. injection of Actrapid (rapid insulin). 1 hour later, the rats were decapitated, and glucose levels in the trunk blood were measured using a commercially available analytical device.

Measurement of hormone concentrations: The concentrations of ACTH and corticosterone were measured using radioimmunoassay.

Immunocytochemistry

C-Fos activation in response to FST was used as a marker of brain activation. Two hours after the beginning of FST or at rest (control animals without any previous test) dams were anesthetized and perfused transcardially. The brains were removed, post-fixed and frozen on dry ice and stored at −80 °C until sectioning. 30 μm sections were cut in the coronal plane on a sliding microtome. After that the immunolabeling was done. After visual inspection and qualitative analysis of fos-like immunoreactivity all over the brain, quantification was done in those nuclei (or sub-regions) considering relevant to the present experiment. Section planes were standardized according to the atlas of Paxinos and Watson (1998) by an experimenter blind to the treatment groups at the same coordinates for each animal. The following brain areas were investigated: PVN (magnocellular, medial and dorsal parvocellular parts), medial and central amygdala (MeA, CeA), mPOA, BNST.

RESULTS AND DISCUSSION

Maternal behavior

Brattleboro AVP- dams spent less time licking-grooming their pups and in arched back posture, an effect not modified by peripheral DDAVP treatment. Thus, the excessive need for water intake did not influence maternal behavior of the AVP-deficient dams. AVP- dams seem to show a pattern of maternal neglect, not doing arched-back or licking–grooming behaviors towards their pups and instead performing just passive, supine nursing. In contrast to undisturbed (naturally occurring) maternal behavior, AVP had no effect on pup retrieval that is a measure of motivational maternal behavior. Because retrieval behavior is initiated by the mother, Terkel classified it as an active maternal response; and they referred to nursing behavior as a passive maternal response since it is primarily initiated by nuzzling and suckling stimulation of the mother's ventral surface by the young. Brain circuitries related to pup retrieval and nursing behavior seems to be different although partially overlapping.

Psychological condition of the mother

During the postpartum period the AVP-deficient rats showed less depressive-like behavior, than the control animals. It was demonstrated by the significantly higher struggling and higher sucrose and saccharin preference. The effect of AVP-deficiency in Brattleboro dams on swimming and struggling behavior was similar to the effect of the antidepressant Reboxetine (selective norepinephrine reuptake inhibitor). The present work showed that AVP- dams drank more sucrose than the other group, and drank more saccharin than the AVP+ mothers, suggesting that they are more resistant to the development of depressive-like behavior. There was no significant difference between the anxiety levels of the genotypes in the EPM test.

Maternal aggression was extremely strong in the early phase of lactation and decreased but remained intense in the late lactation period. The AVP-deficiency caused suppressed maternal aggression in both early and late phases of lactation; violent forms of attack were decreased in the latter but not the former phase.

In lactating females, AVP deficiency did not alter learning, but led to decreased impulsivity. The lactation-induced increase in impulsivity was abolished by AVP deficiency in lactating females. Chlordiazepoxide-induced facilitation of GABAergic

led to increased impulsivity only in AVP-deficient dams and imipramine-induced enhancement of serotonergic activity, which decreases impulsivity in the literature, but increased the choice impulsivity of the AVP- dams. Taken together, AVP appears to play a role in the regulation of impulsivity exclusively during lactation: it has an impulsivity increasing effect which is potentially mediated via stress axis-dependent mechanisms and fine-tuning of GABAergic and serotonergic function.

Stress-axis:

Elevated adrenal gland mass, increased mRNA levels of CRH in the PVN and resting plasma corticosterone levels were observed in AVP+ mothers. Interestingly, AVP- mothers failed to exhibit an increase in body mass, adrenal gland hyperplasia, or increased CRH mRNA and resting corticosterone levels.

The induction of anaphylactoid or hypoglycemic responses by the administration of egg white and insulin, respectively, were paralleled by elevated ACTH and corticosterone levels, but these effects were smaller in mothers vs virgins and blunted in AVP- vs AVP+ rats. These results suggest that AVP may play a significant role in the maintenance of the resting HPA axis hyperactivity in dams, but its role in HPA axis reactivity might not be more pronounced in dams when compared with that in virgins.

Immunocytochemistry

Under basal conditions, AVP-deficient mothers had more c-Fos expression in the mPOA, PVN (magnocellular, dorsal and medial parvocellular parts) and the ce CeA and MeA, but not in BNST. In these areas the swim-stress-induced activation was smaller.

The higher basal activity of magnocellular cells of AVP- rats could be a possible consequence of the constant osmotic pressure. The homeostatic imbalance of the AVP-deficient rats might lead also to an activation of the dorsal parvocellular PVN, as the autonomic center. The CeA is important in adaptation to chronic somatic stressors, while MeA is related to the regulation of the response to emotional stress. The resting c-Fos levels of the AVP-deficient rats could be more enhanced in the CeA than in MeA due to the somatic stress of the diabetes insipidus.

CONCLUSIONS

Based on our findings we can conclude the followings:

(1) We confirmed the important role of AVP in the development of undisturbed maternal response via central mechanism, which clearly dissociated from the separation-induced maternal retrieving, where AVP had no effect.

(2) The AVP can attenuate the development of a depressive-like phenotype, increase abnormal maternal aggression and impulsivity.

(3) The endogenous AVP supports the changes in resting HPA axis activity during lactation that mimic - partially - those observed under chronic stress conditions and the AVP-deficiency results in a blunted HPA axis response of the mothers to different acute stressful stimuli.

(4) The lack of AVP results in higher basal neuronal activity at a lot of brain regions, with a lower stress induced c-Fos activation.

SUMMARY

Early mother-infant relationship is an important factor in the psychosomatic development of the offspring. Postpartum depression and stress can arrest normal parental bounding. Vasopressin (AVP) is a key regulator both of social and depression-like behavior and might have a role in stress regulation.

We aimed to clarify if the congenital lack of vasopressin (AVP) influences maternal behavior paralleled by the development of a depressive-, and anxiety-like phenotype, changes in maternal aggression and impulsivity and the activity of the HPA axis during lactation using AVP-deficient Brattleboro rats.

Our results demonstrated that the congenital deficit of AVP in Brattleboro rats reduced the spontaneous maternal behavior without affecting the induced maternal response. AVP- mothers showed more preference for sucrose and saccharin and struggled more in the forced swim test, suggesting that they act as less depressive without any changes their anxiety levels. AVP-deficient mothers had suppressed maternal aggression. The lactation-induced increase in impulsivity was abolished by AVP-deficiency. AVP seems to contribute to the physiological changes observed during lactation mimicking a chronic stress state, because in AVP-deficient dams, adrenal gland hyperplasia and resting corticosterone level elevations were not observed. The

acute HPA axis stimulation was blunted in lactating rats compared with the virgins and in AVP-deficient rats compared with the controls. Under basal conditions, AVP-deficient mothers had more c-Fos positive cells, but the swim-stress-induced activation was smaller.

In conclusion, AVP-deficiency resulted in maternal neglect due to a central effect, suppressed maternal aggression and impulsivity and was protective against depressive-like behavior probably as a consequence of reduced activation of some stress-related brain structures. Although the present data on mood suggest that AVP antagonists might have positive impact on postpartum depression, the negative side effects on maternal behavior may limit their usage.

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