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Chronic Postnatal Stress Induces Depressive-like Behavior in Male Mice and Programs second-Hit Stress-Induced Gene Expression Patterns of OxtR and AvpR1a in Adulthood

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Abstract Chronic stress (CS) during early life represents a major risk factor for the development of mental disorders, including depression. According to the Two/Multiple-Hit hypothesis, the etiology of neuropsychiatric disorders usually involves multiple stressors experienced subsequently during different phases of life. However, the molecular and cellular mechanisms modulating neuronal and behavioral changes induced by multiple stress experiences are just poorly understood. Since the oxytocinergic and vasopressinergic systems are neuroendocrine modulators involved in environmentally driven adaptations of stress sensitivity we hypothesized that postnatal CS programs oxytocinergic and vasopressinergic receptor expression changes in response to a second stress exposure in young adulthood. First we investigated if postnatal CS (maternal separation + social isolation) induces depressive-like behavior and alters oxytocin receptor (*OxtR*) and arginine vasopressin receptor type 1a (*AvpR1a*) gene expression in the hippocampus (HC) of male mice and (2) if a second single stressor (forced swimming, FS) in young adulthood affects gene expression of *OxtR* and *AvpR1a* at adulthood dependent on CS pre-experience. We found that postnatal CS induced depressive-like behavior and enhanced AvpR1a expression in HC at young adulthood. Moreover, in line with our hypothesis, only combined stress exposure (CS + FS), but not CS or FS alone, resulted in increased gene expression of *OxtR* in HC at adulthood. In contrast, AvpR1a expression was decreased in both adult FS and CS + FS animals. Overall, our results provide evidence that CS programs neuroendocrine systems and thereby influences stress responses in later life periods.

Keywords Early-life stress · Depression · Limbic · Two-hit · Neuropeptide

Introduction

Perinatal adverse experiences critically influence the maturation of brain structure and function and therefore represent a major risk factor for the development of psychopathological behavior, such as depression, in later life periods [1–7]. In this context it has to be considered that the environmentally driven development of psychopathologies is a multistep process, as stated in the cumulative or diathesis stress hypothesis [8–12]. Based on this classical theory, the Two- (or Multiple-) Hit concept proposes that neuropsychiatric diseases are the result of two (or more) stressors experienced over the lifespan. In this model it is hypothesized that adverse events, such as childhood trauma or chronic stress, exert programming effects on the nervous system, which in consequence predisposes an individual to develop stress-related disorders in response to second or multiple stress exposures during later life [13–20].

Several studies have shown that early postnatal adverse experiences, such as maternal separation or chronic stress, can result in depressive-like behavior in adulthood as well as in enhanced stress sensitivity/reactivity [5, 19, 21–24]. Furthermore, traumatized individuals tend to show deficits/difficulties in behavioral stress coping strategies during stressful situations (second hit events) later in life [21].

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There is emerging evidence that the impact of adverse life events on the development of stress responsiveness and sensitivity not only depends on the function of the classical stress hormones such as ACTH and CORT, but is also modulated by the hypothalamic hormones oxytocin (Oxt) and arginine vasopressin (Avp) [25–29]. It is assumed that a well-balanced interplay between the two systems is crucial for the functional activity of hypothalamic and limbic circuitries and thereby important for the regulation of stress responses and emotional behavior [30, 31].

Oxt and Avp are released into the blood stream by magnocellular neurons in the hypothalamic supraoptic and paraventricular nucleus. In addition, Oxt and potentially also Avp neurons target a number of brain areas directly via axonal contacts, in particular areas, which are implicated in reward (VTA, NAc, mPFC), stress (hippocampus, amygdala) and maternal behavior (olfactory bulb, BNST, MPOA) [30, 32]. The neuronal effects are mediated by their respective receptors, the oxytocin receptor (OxtR) and the arginine vasopressin receptor type 1a and 1b (AvpR1a, AvpR1b) [33, 34]. In the present study, we focused on the hippocampus (HC), an area involved in the regulation of the stress response and emotional behavior and where both OxtR as well as AvpR are quite numerous [35]. Moreover, the development and maturation of the hippocampus appears to be particularly sensitive to the quality of parental care [36] and acute and chronic stress exposure [19, 20]. Additionally, it is known that gene expression in the HC can be altered by a variety of different stressors [37] but it still remains unclear how and to which extent these changes endure beyond a stressful experience and can be altered by further stressors during lifetime.

Thus, the aim of the present study was to test the hypotheses (1) that postnatal CS induces depressive-like behavior and in parallel alters the expression of *OxtR* and *AvpR1a* expression in the HC and (2) that postnatal CS might alter the susceptibility of the Oxt and Avp systems towards a second stress experience later in life.

Material and Methods

Animals

C57BL/6 mice (Taconic Biosciences A/S, Denmark) were housed on a 12-h light-dark cycle with access to water and food ad libitum. Home cages containing nesting material were cleaned once a week in order to minimize handling-induced stress. After birth of the pups (defined as postnatal day 0; PND 0) the home cages were not cleaned during the first two weeks to reduce stress for dams and pups. The experimental protocols were approved by the ethics committee of the government of the state of Saxony-Anhalt according to the German guidelines for the care and use of animals in laboratory research (§8 TSchG; AZ: 42,502–2-1272).

Stress Paradigm

Control (CON)

Pups were reared together with their mother without disturbance except of the above-mentioned cleaning routine. After weaning at PND 21 the offspring were housed together in same-sex groups with up to 5 individuals until the time of the respective experiment.

Chronic Postnatal Stress (CS; "1st Hit")

Chronic stress was applied by combining daily maternal separation from PND 1 to PND 21, and subsequent rearing in social isolation. For maternal separation, pups were removed from the home cage and isolated individually in boxes of a size of 13 × 13 cm for 3 h (09:00–12:00 a.m.), allowing for auditory and olfactory, but not for body contact. For separation during the first week the isolation boxes were placed in a humidified incubator at 32 °C. During separation the dam remained in the home cage but all nesting material was removed. Upon return of the pups new nesting material was provided. On PND 21 animals were weaned 2 h after the last separation and housed individually until the time of the respective experiment.

Forced Swimming (FS; "2nd Hit")

Forced swimming at young adulthood (details see below) served as second stressor ("2nd hit") and was additionally used to test for depressive-like behavior.

Male animals of the control and the CS group were randomly assigned to the following experimental groups. The developmental periods "young adulthood" (PND 62–64) and "adulthood" (PND 100) were defined after Olazábal [38].

PND 64 CON: Young adult control animals (PND 64) not exposed to any stressor.

PND 64 CS: Young adult animals (PND 64) exposed to CS.

PND 100 CON: Adult control animals (PND 100) not exposed to any stressor.

PND 100 CS: Adult animals (PND 100) only exposed to CS.

PND 100 FS: Adult animals (PND 100) only exposed to forced swimming at young adulthood.

PND 100 CS + FS: Adult animals (PND 100) exposed to ELS ("1st hit") and forced swimming ("2nd hit") at young adulthood.

Behavioral Tests

In order to test if CS induces a depressive-like phenotype, the animals were tested for two depressive-like behaviors: (1) learned helplessness, indicated by increased floating time during forced swimming compared to controls and (2) anhedonia, indicated by reduced consumption of sucrose solution during the sucrose preference test compared to controls.

Forced Swimming (FS)

Forced swimming to test for learned helplessness was performed on PND 62 and 63. On both days the animals were placed into a glass tank filled with water at 22 °C and forced to swim for 15 min (habituation). Afterwards they were returned to the home cage for 24 h. On the second day behavior was videotaped and the duration of active swimming and passive floating during the first 5 min of the test was analyzed (Noldus, Observer XT software, Wageningen, Netherlands). Results of individual animals were used for analysis.

Sucrose Test (SPT)

The sucrose preference test was performed at PND 77–80 in the animals´ home cages. One the first day animals were provided with two bottles of water for habituation and to determine the side preference (measured as higher volume of consumed water). On the second day, water bottles were weighed and the water bottle on the less preferred side was replaced by a bottle containing 4 % sucrose. Sucrose solution was available for the animals for 48 h. Sucrose preference was determined by calculating the consumed volumes per animal. Litter means were used for analysis.

Gene Expression Analysis

Male animals of all experimental groups were sacrificed by decapitation on PND 64 and PND 100, respectively. Left and right HC were dissected and immediately frozen in liquid nitrogen. RNA extraction of one hemisphere was performed using the RNeasy Mini kit (QIAGEN GmbH, Hilden, Germany). Genomic DNA was removed using the RNase-free DNase kit (QIAGEN GmbH, Hilden, Germany).

Analysis of RNA samples was performed using the Multiplex RT-PCR Kit (QIAGEN GmbH, Hilden, Germany), allowing to perform simultaneous one-step quantitative real-time PCR of 2 to 5 target genes using TaqMan gene expression assays (Life Technologies, Carlsbad, California, United States). Commercially available assays for the oxytocin receptor (OxtR; Mm01182684_m1; FAM), and the arginine vasopression receptor type 1a (AvpR1a; Mm00444092_m1; FAM) as target genes and hypoxanthine phosphoribosyltransferase I (Hprt I; Mm01545399_m1; VIC) as reference gene, were used. Gene expression of *OxtR*, *AvpR1a* and *Hprt* in the HC was calculated using the delta-delta CT method and samples were normalized to their respective control groups. Data present the analysis of individual animals.

Statistics

Results of the behavioral and gene expression analysis were tested for significance using two-sided unpaired t-test. Data from gene expression analysis were normalized to controls.

Data are presented as means + SEM. Significance value was set as follows: * $p \leq 0{,}05$; ** $p \leq 0{,}01$. Graphs were made using GraphPad Prism 6.0 software (GraphPad, LaJolla, California, United States).

Results

Behavior

Chronic Stress Induces Depressive-like Behavior at Young Adulthood

Male CS animals displayed significantly more time floating ($p = 0.015$; Fig. 1a) and less sucrose consumption ($p = 0{,}007$; Fig. 1b) compared to control males reflecting enhanced depressive-like behavior.

Gene Expression

A) Oxytocin receptor

No significant differences in *OxtR* gene expression could be detected in young adult CS animals (PND 64 CS; Fig. 2a).

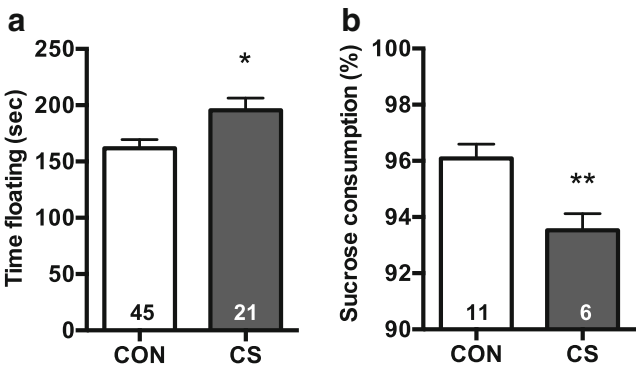

Fig. 1 Depressive-like behavior during forced swimming and sucrose preference test. Postnatal CS animals displayed depressive-like behavior indicated by longer floating times during forced swimming (Fig.1a) and reduced sucrose consumption (Fig.1b) compared to controls. N numbers are indicated in the respective columns. * $p \leq 0.05$; ** $p \leq 0.01$

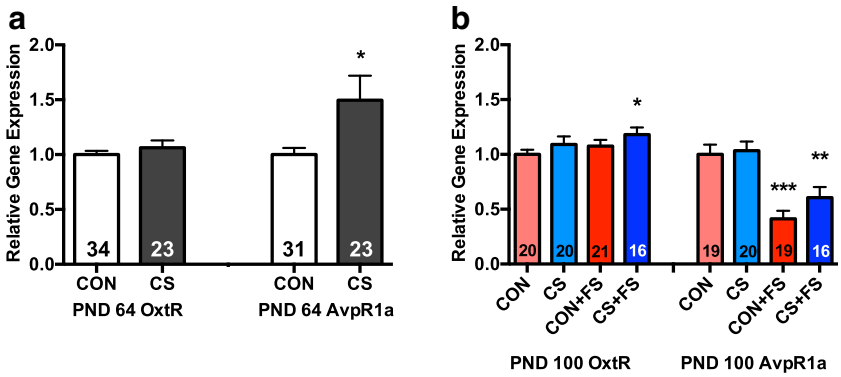

Fig. 2 *OxtR* and *AvpR1a* gene expression in HC. **a**: Postnatal CS induced a transient increase of *AvpR1a* but not *OxtR* expression in the HC at young adulthood (PND 64). **b**: Only the consecutive exposure to postnatal CS and FS led to increased *OxtR* expression in HC at adulthood (PND 100). *AvpR1a* expression was reduced by FS alone as well as by CS + FS. N numbers are indicated in the respective columns. * $p \leq 0.05$; ** $p \leq 0.01$

In adult animals only the consecutive exposure to CS as "first hit" and FS as "second hit" (PND 100 CS + FS), but neither CS (PND 100 CS) nor FS (PND 100 FS) alone, resulted in significant increases of *OxtR* (p = 0,02, Fig. 2b).

B) Arginine vasopressin receptor type 1a

T-test revealed that *AvpR1a* expression in the HC of young adult CS animals (PND 64 CS) was significantly increased compared to controls (p = 0,02; Fig. 2a). This effect was not detectable anymore in adult CS animals (PND 100 CS; Fig. 2b). However, adult animals subjected to FS (PND 100 FS) or CS + FS (PND 100 CS + FS) displayed significantly decreased *Avpr1a* expression compared to naive controls (p < 0,001; p = 0,005, respectively; Fig. 2b).

Discussion

Adverse experiences during early life periods can program an individual's sensitivity, responsiveness and reactivity towards stressful events later in life. The present study in male mice revealed that exposure to CS in early life induced depressive-like behavior paralleled by a transient increase of *AvpR1a* gene expression in the HC at young adulthood, which is supporting the concept that early adversities can interfere with behavioral and brain functional development. Furthermore, our data indicate that CS exerts a long-term programming impact on changes of *OxtR* and *AvpR1a* gene expression in response to a second stressor later in life: Only CS combined with a subsequent second stress exposure (FS) at young adulthood, but neither CS nor FS alone, induced elevated *OxtR* gene expression in the HC at adulthood. In contrast, AvpR1a expression was reduced by FS alone, an effect that was slightly alleviated by pre-exposure to CS.

Oxt and Avp have been shown to exert regulatory effects on the hypothalamic-pituitary-adrenal (HPA) axis, the major stress response system. The modulatory action is based on a functional interplay between Oxt and Avp and it is proposed that they mediate opposing effects [30]: whereas Oxt release is thought to be associated with an attenuation of stress-induced HPA axis activity [39] and thereby linked to anxiolytic and antidepressive functions [40], Avp may act in opposite direction exerting anxiogenic and depressive functions [41].

Both neuropeptides are released peripherally into the bloodstream and can thereby modulate brain [30] and cardiovascular [42] functions in a hormone-like manner. In addition, these neuropeptides also exert direct actions in multiple brain regions via axonal and dendritic release [31, 43–46]. The central effects of Oxt and Avp in the brain are mediated by their respective receptors, OxtR and AvpR1a, which are expressed in a number of brain regions including cortical and limbic areas that are involved in the control of emotional and social behaviors [33, 34]. In the hippocampal formation OxtR are found predominantly on the soma and on dendrites of GABAergic interneurons and it has been shown that their activation increases the firing rate of the interneurons resulting in suppressed activity of pyramidal neurons [47, 48] and in enhanced cortical information transfer while simultaneously lowering background activity and improved information processing [49]. Similarly, Avp fibers as well as AvpR1a receptors are present in all areas of the hippocampal formation [50]. Avp fibers make asymmetric (presumably excitatory) synaptic contacts with pyramidal neuron dendrites, dendritic spines and with axonal spines, while on interneuron dendrites they make symmetric (presumably inhibitory) synaptic contacts [50].

CS Induces Depressive-like Behavior and Elevates Hippocampal AvpR1a Gene Expression

The depressive-like behaviors, i.e. symptoms of learned helplessness and anhedonia, observed in young adult CS-exposed animals were paralleled by elevated *AvpR1a* gene expression in the HC at this age. This is in line with findings from a receptor binding study demonstrating that maternal separation stress resulted in increased AvpR1a receptor binding in the dentate gyrus of adolescent male rats [51]. The elevated *AvpR1a* gene expression in our CS exposed animals may be

at least in part responsible for the observed depressive-like behavioral symptoms since it was shown that Avp can evoke anxiogenic actions and thereby increase anxiety- and depression-related behaviors [30]. Moreover, it is tempting to speculate that the upregulation of hippocampal *AvpR1a* gene expression may result in hippocampal hyperexcitability and thereby might sensitize the responsiveness of this brain region towards a second stressor. This is supported by studies showing that Avp-induced long-term potentiation may lead to a long-lasting enhancement of hippocampal excitability [52, 53], which on the brain systems level may lead to dysfunctional limbic pathways.

CS Programs Oxt and Avp Receptor Changes in Response to a Second Stressor at later Life Periods

In contrast to the findings in young adulthood no changes of *AvpR1a* expression could be detected in adult animals after chronic stress, indicating a transient overexpression of these receptors. A study by Gray et al., (2012) could show that the central arginine vasopressin V1a receptor is mediating the normal habituation of the HPA axis responses to repeated stress exposure [54]. Therefore, it is possible that the transient overexpression of AvpR1a is also due to a habituation effect mediated by Avp itself. However, *AvpR1a* expression in adult animals was significantly decreased by FS alone as well as by the exposure to FS + CS, although the effect was slightly alleviated in the CS + FS animals. Several studies have shown that forced swimming triggers the activation of the brain AVP system resulting in increased release of AVP in several subregions [55, 56]. To regulate the stress response adequately, a counter-regulation of the Avp receptor density might be a possible explanation for the reduction in *AvpR1a* gene expression.

While CS or FS alone did not alter *OxtR* expression in adult animals, the combination of both stressors resulted in increased expression of this receptor in the HC. It is tempting to speculate that this effect may be an adaptive response to alterations in Oxt release during the 2nd stress experience. Evidence for this interpretation is derived from studies reporting that forced swimming enhances hypothalamic Oxt release, an effect that was amplified by repeated stress exposure [41, 56]. These findings can be interpreted within the framework of the cumulative or diathesis-stress-model, which is based upon the assumption that individual genetic traits/polymorphisms in interaction with environmental factors, including stress, define an individual's predisposition and susceptibility towards stressful events throughout life [8, 10, 11, 18]. A recent study by Gray et al. [37] investigated the effects of chronic stress when paired with a novel stressor and could show that changes in gene expression patterns were significantly different depending on the history and type of stress experience: naive single stressors led to different gene expression activation patterns than a combination of different stressors indicating that a history of stress can indeed permanently alter stress susceptibility and gene expression patterns in the hippocampus [37].

Moreover, the programming effect of CS, as found in our study, may be viewed within the context of the hormonal imprinting hypothesis [57], which assumes that the first encounter between a hormone and its developing target cell receptor, particularly when this occurs during sensitive perinatal phases, determines and programs hormone production, receptor-binding and signal transduction capacity at later life periods [58–60]. However, the detailed mechanisms, particularly the epigenetic regulation, of these hormonally induced programming effects have to be investigated in further studies.

Taken together our study provides further evidence that the pathophysiology of neuropsychiatric disorders, such as depression or disturbed stress coping later in life, may be caused by a combination and interaction of multiple stressors experienced throughout different life periods.

ACTH, adrenocorticotropin-releasing hormone; Avp, arginine vasopressin; AvpR1a/b, arginine vasopressin receptor type 1a/b; BNST, bed nucleus stria terminalis; CON, control; CORT, corticosterone; CS, early-life stress; FS, forced swimming; HC, hippocampus; HPA, hypothalamic-pituitary-adrenal axis; Hprt, hxpoxanthine phosphoribosyltransferase; mPFC, medial prefrontal cortex; MPOA, medial preoptic area; MS, maternal separation; NAc, nucleus accumbens; SPT, sucrose preference test; Oxt, oxytocin; OxtR, oxytocin receptor; PND, postnatal day; VTA, ventral tegmental area.

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