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Gestational stress in mouse dams negatively affects gestation and postpartum hippocampal BDNF and P11 protein levels☆

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ABSTRACT

Stress during pregnancy increases the risk to develop psychological disorders such as depression during pregnancy or in the postpartum period. According to the neurotrophin hypothesis of depression, the pathophysiology of depression is caused by reduced neurotrophic activity in the brain. However, most studies only focus on the molecular changes happening to the offspring upon gestational stress. To gain insight into the potential molecular changes happening in the stressed dams, C57Bl6/J mice were stressed during their first week of gestation. At 28 days postpartum, the hippocampus and nucleus accumbens core of the dams, two brain regions heavily implicated in depression, were evaluated using immunohistochemistry to detect changes in the neurotrophin system. Gestational stress decreased the weight of the dams, increased the chance for spontaneous abortion and increased the weight of offspring. Litter size, survival rates and sex distribution were not altered as a consequence of gestational stress. Hippocampal brain-derived neurotrophic factor (BDNF) decreased following exposure to stress during pregnancy. Hippocampal protein levels of p75^{NTR}, a low-affinity receptor for BDNF which can induce apoptosis, were increased following exposure to stress. Protein levels of p11, of which the expression is regulated by BDNF, were decreased in the hippocampus. No changes were found for TrkB immunostaining or apoptosis. Taken together, this shows that stress during pregnancy negatively affects the neurotrophin system in the hippocampus of the dams, thereby reducing hippocampal plasticity. These data confirm that gestational stress has a negative impact on pregnancy.

1. Introduction

Pregnant women exposed to chronic or excessive stress have an increased risk for developing stress-related psychological disorders during pregnancy or in the postpartum period (Gavin et al., 2005; Oberlander et al., 2006). Likewise, rat dams experiencing daily restraint stress during pregnancy develop increased depression-like and anxiety-like behavior following birth of the litter (Baker et al., 2008; Darnaudery et al., 2004; J. W. Smith et al., 2004) and show changes in stress hormone secretion and body weight during pregnancy (Baker et al., 2008; Darnaudery et al., 2004; J. W. Smith et al., 2004; van den Hove et al., 2011). It is clear from this literature that gestational stress (GS) negatively affects behavior and the physiology of the dam during and after pregnancy.

GS modulates physical and psychological development and may impair mood and behavior in the offspring in later life causing higher risks for disorders like autism and depression (Kinney et al., 2008; Rice et al., 2007). Likewise, GS is linked with high anxiety, depression-like behavior, and learning and memory deficits in rodent offspring (Gue et al., 2004; J. W. Smith et al., 2004; van den Hove et al., 2011; Zuena et al., 2008). Physiologically, GS can cause aberrant birth weights and a predisposition towards obesity either developmentally or later in life

Abbreviations: BDNF, brain-derived neurotrophic factor; CA, cornu ammonis; DB, diagonal band of Broca; DG, dentate gyrus; E, embryonic day; GS, gestational stress; HDB, horizontal limb of diagonal band of Broca; MS, medial septum; Nac, nucleus accumbens; P, postnatal day; TBS, tris-buffered saline; TBS-T, tris-buffered saline with 0.3% Triton-X100; TUNEL, terminal deoxynucleotidyl transferase dUTP nick-end labeling; VDB, vertical limb of diagonal band of Broca; VTA, ventral tegmental area

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(Mueller and Bale, 2006).

Stress-induced reductions in neurotrophins may contribute to the pathophysiology of depression (Duman et al., 2000; Jacobs et al., 2000). Indeed, brain-derived neurotrophic factor (BDNF) has been implicated in depression and in antidepressant action (Monteggia et al., 2007; Pandey et al., 2008; Taliaz et al., 2011). The complex actions of BDNF are attributed to its receptors TrkB and $p75^{NTR}$. The proneurotrophin receptor $p75^{NTR}$ induces apoptosis, while TrkB induces synaptogenesis and neurogenesis (Pang et al., 2004). In contrast to its antidepressant effects in the hippocampus, rodent studies have demonstrated pro-depressant functions for BDNF in the ventral tegmental area (VTA)-nucleus accumbens (NAc) (Berton et al., 2006; Eisch et al., 2003; Taliaz et al., 2013). Regional expression patterns of its receptors may contribute to the different actions of BDNF (Martinowich et al., 2007). Interestingly, BDNF regulates expression of p11 which is involved in the cell surface localization and signal transduction of serotonin receptor subtypes 1B/4, suggesting that p11 may also play a role in the pathophysiology of depression and in antidepressant action (Alexander et al., 2010; Egeland et al., 2010; Svenningsson et al., 2006; Warner-Schmidt et al., 2009).

GS is mainly used as a depression model for the offspring, yet the effects of this stress exposure on the neurotrophic system of the dams remains elusive. We studied whether GS influences the neurotrophic balance in the hippocampus and NAc core in the dams, hypothesizing that GS reduces BDNF and p11 protein levels in the hippocampus and increases them in the NAc core. We further hypothesize that GS causes a shift in the $p75^{NTR}$/TrkB expression ratio.

2. Material & methods

2.1. Animals and prenatal stress

Female C57BL/6 mice (Charles River, L'Arbresle, France) at 8–12 weeks of age were used in this study. All animals were housed under a 12 h light/dark cycle (lights off at 7:00 A.M.) with an average temperature of 22 °C and relative humidity of 42%. Food and water was provided ad libitum throughout the study. All studies were executed according to protocols approved by the local Animal Ethical Committee of Maastricht University, Maastricht, The Netherlands, and met governmental guidelines (UM-DEC 2009–110).

Presence of a copulation plug was considered as embryonic day 0 (E0). Subsequently, the female was housed individually, given tissues for nest building, and weighed at E0, E7 and E14. Pregnant females were assigned to a control ($n = 22$) or GS ($n = 40$) group, with more females being placed in the GS group because previous studies showed increased abortions in mice stressed during early pregnancy. The prenatal stress paradigm was performed as described previously (Sierksma et al., 2012). In short, pregnant females assigned to the GS group were subjected to chronic restraint stress by placing the mouse in a 5 cm diameter glass cylinder and positioned underneath a bright light. The glass cylinder was filled with a layer of water with a height of 1 cm. This was done to increase the discomfort of the animals, since the small layer of water made the animals wet. Restraint stress was performed 3 times per day (at approximately 8:00 A.M.; 12:00 A.M.; 16:00 A.M.), for 45 min per session from E1 to E7. After each restraint stress session, the animals were placed back into their home cage. Control mice were left undisturbed in their home cage.

2.2. Tissue preparation

After weaning at postnatal day 28 (P28), dams were deeply anesthetized with sodium pentobarbital (60 mg/kg; CEVA, Libourne, France) and intracardially perfused with ice-cold Somogyi fixative (4% paraformaldehyde, 15% picric acid, and 0.05% glutaraldehyde in 0.1 M phosphate buffer, pH 7.6). Brains were dissected, fixated in the same fixative without gluteraldehyde for 2 additional hours and washed overnight in 0.1 M phosphate buffer. Subsequently, brains were immersed in sucrose solution at 4 °C during two overnight steps in 10% and 20% sucrose (in 0.1 M phosphate buffer), respectively. Brains were snap-frozen with CO_2 and stored at −80 °C. Coronal sections of 30 µm were cut at −25 °C and stored at −80 °C for immunohistochemistry.

2.3. Immunohistochemistry

Protein levels of BDNF, $p75^{NTR}$, TrkB and p11 were analyzed in the hippocampus (CA1, CA3 and DG region) and NAc core. In addition, $p75^{NTR}$ was also analyzed in the medial septum (MS) and diagonal band of Broca (DB, vertical VDB and horizontal HDB), as this is the main site for $p75^{NTR}$ production. Apoptosis in the hippocampus was analyzed by means of terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL). BDNF/p11 and $p75^{NTR}$/TUNEL were performed as double staining using Hoechst as counterstain.

All washing steps were performed in Tris-buffered saline/Tween-20 (TBS-T), Tris-buffered saline (TBS) and TBS-T for 3 times 10 min at room temperature. After washing, sections were incubated with the following primary antibodies in TBS-T overnight at 4 °C: rabbit anti-BDNF (AB1534SP from Chemicon, Billerica, MA; 1:400) (Zermeno et al., 2009), rabbit anti-TrkB (#4606 from Cell Signaling Technology, Beverly, MA; 1:100), rabbit anti-$p75^{NTR}$ (#07-476 from Millipore, Billerica, MA; 1:2000) (Cragnolini et al., 2009) or goat anti-p11 (AF2377 from R&D Systems, Abindon, UK; 1:1000) (Schmidt et al., 2012). After washing, sections were incubated for 2 h at room temperature with donkey anti-rabbit Alexa-488 (#A-21206 from Invitrogen, San Diego, CA; 1:100) in TBS-T. TUNEL staining was performed as described previously (De De Vry et al., 2010) using the TUNEL reaction buffer kit (Roche, Basel, Switzerland) and streptavidine-Alexa-Fluor-594 (#S-11227 from Invitrogen, 1:2000 in TBS-T). Nuclear counterstaining was performed by washing sections three times with TBS at room temperature for 5 min, followed by 30 min incubation at room temperature with Hoechst dye #33342 (Sigma-Aldrich; 1:500 in TBS). Additional validation of the primary antibody specificity was done by western blot analysis and a negative control immunohistochemical staining without primary antibody.

2.4. Immunohistochemical analysis

Depending on the brain region of interest, slightly different methods were used for quantification. For immunohistochemical analysis of the dorsal hippocampus, 3 unilateral sections were analyzed per animal (Bregma −1.34 mm to −2.54 mm). Per section, 9 photomicrographs were analyzed (3 in each subregion: DG, CA3 and CA1). For analysis of the NAc, 4 unilateral sections per animal were analyzed (Bregma +1.7 mm to +0.86 mm). Per section, 6 photos were analyzed in the NAc core surrounding the anterior commissura. Analysis of $p75^{NTR}$ immunostaining was also performed in the MS and DB, the main sites where $p75^{NTR}$ is produced. Analysis of the MS/DB was done in 6 sections per animal (Bregma +1.18 mm to +0.02 mm). For the first 4 sections, 3 photos were taken per section (1 MS, 1 left DB, 1 right DB), while 2 photos per section were taken for the last 2 sections (1 left DB, 1 right DB). A photomicrograph was taken at each selected site with a digital camera (F-view; Olympus, Tokyo, Japan) attached to an Olympus AX-70 microscope. Immunoreactivity was analyzed by measuring the mean grey values in hand drawn regions of interest (ROIs, Supplementary table S1), corrected for the background, using ImageJ (Wayne Rasband, National Institutes of Health, Bethesda, MD). For analysis of TUNEL staining in the hippocampus, TUNEL and Hoechst double-positive apoptotic cells were counted in 4 sections per animal. Apoptotic cells were counted in the DG and entire CA (CA1 and CA3) separately, for both hemispheres.

2.5. Statistics

The odds of having a full-term pregnancy after observation of a copulation plug was statistically analyzed with a Chi-square analysis. Litter size and sex distribution of the litter, as well as the immunohistochemistry data were analyzed by a two-tailed Student *t*-test. Weight gain of the dams during pregnancy was analyzed with a two-way 3 × 2 ANOVA time (E0, E7, and E14) × treatment (stress vs control), while weight differences at given time points were analyzed by a Sidak's multiple comparisons test. Weight of the offspring at P28 was analyzed by a two-way ANOVA with the factors treatment and sex. Of note, only dams that successfully delivered pups were included in the analysis of weight gain and for immunohistochemistry. Significance was set at $p < 0.05$ for all analyses. SPSS 16.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. All data are presented as means + SEM. Graphs were created using GraphPad Prism 4 (GraphPad Software, La Jolla, CA).

3. Results

3.1. GS negatively affects pregnancy

Weight of the pregnant dams was measured during pregnancy at E0, E7 and E14. Dams were distributed over the experimental groups in such a way that both groups had similar average starting weights. The weight of the animals increased significantly over time ($F(1,28) = 7.52$, $p < 0.05$) and differed with treatment ($F(1,30) = 7.592$, $p < 0.01$; Fig. 1a). Stressed dams weighed significantly less than control dams at E7 ($t(84) = 4.64$; $p < 0.001$) and E14 ($t(84) = 3.52$; $p < 0.01$). In the control group, 82.5% of the dams with a vaginal plug successfully delivered offspring, in contrast to a mere 42.2% of the dams that were stressed during early gestation (Table 1). A Chi-square analysis showed that GS decreases the odds for full-term pregnancy approximately two-fold ($\chi(1) = 14.465$, $p < 0.001$).

3.2. GS increases weight of the offspring

Litter size and weight of the offspring was measured to investigate whether early prenatal stress influences these outcomes. Litter size did not differ between control and stressed groups at birth (P0) ($F(1,28) = 2.059$, n.s.) or 28 days later (P28) ($F(1,28) = 2.207$, n.s.) (Table 1), and no correlations were found between litter size and offspring weight at these time points, independent of stratification for sex (data not shown). Postnatal survival rate of the offspring was not affected by GS ($F(1,28) = 0.024$, n.s.), nor was the sex distribution of the offspring at P28 (# males: $F(1,28) = 2.020$, n.s.; # females: $F(1,28) = 0.008$, n.s.; % males: $F(1,28) = 0.413$, n.s.). Weight of the offspring was measured at P28 and analyzed by two-way ANOVA with the factors treatment and sex (Fig. 1b). There was a significant effect of treatment ($F(1,159) = 40.070$, $p < 0.001$), sex ($F(1,159) = 37.634$, $p < 0.001$), and a significant sex*treatment interaction effect ($F(1,159) = 7.482$, $p < 0.01$). Early GS significantly increased weight of the offspring, while female offspring weighed significantly less than their male littermates in control and stress groups.

3.3. Molecular changes in the NAc core and hippocampus of GS dams

BDNF immunoreactivity was assessed in the DG, CA1 and CA3 of the hippocampus and in the NAc core of control and stressed dams. Stress significantly decreased BDNF immunoreactivity in the hippocampus ($p < 0.05$) but not in the NAc core (Fig. 2a–b, 3a–b). Further analysis showed that this stress-induced decrease in hippocampal BDNF was particularly pronounced in the CA1 ($p < 0.05$) and DG ($p < 0.05$) of the hippocampus, but not in the CA3.

Immunoreactivity of the $p75^{NTR}$ receptor was assessed in the various subregions of the hippocampus in control and GS dams.

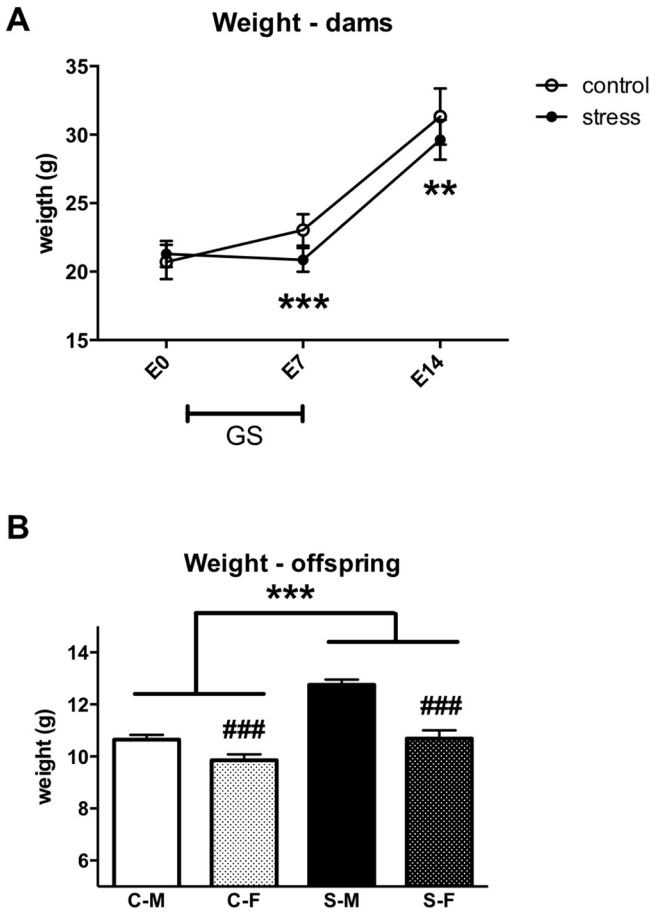

Fig. 1. (a) Effect of GS on weight of the pregnant dam. On day E0, before stressed has been applied, the weight is the same in both groups. During pregnancy at E7 and E14, weight gain of stressed dams is lower compared to controls (n = 16 per group). (b) Weight of male and female offspring of control ($n = 84$) and stressed ($n = 79$) dams at P28. GS increases offspring weight compared to controls, and females weigh significantly less than males. In addition, a sex*treatment effect on weight is found. Data are shown as mean with SEM. Significant differences between stressed and control groups are marked with $^{**}p < 0.01$ or $^{***}p < 0.001$. Significant differences between male and female groups are marked with $^{\#\#\#}p < 0.001$. C-M is control male, C-F, control female, S-M, stress male and S-F, stress female.

Immunoreactivity was significantly increased in the hippocampus ($p < 0.01$). Further analysis showed that $p75^{NTR}$ was specifically increased in the DG ($p < 0.05$) and CA3 ($p < 0.01$), though not in the CA1 (Fig. 2c–d, 3c). No differences in $p75^{NTR}$ immunoreactivity were found in the MS and DB (Fig. 3d). As no $p75^{NTR}$ immunoreactivity was observed in the NAc core, this nucleus was excluded from further analysis.

TrkB immunoreactivity in the hippocampus and NAc core was analyzed in control and GS dams. Stress during pregnancy did not significantly alter TrkB protein levels in any of the analyzed brain structures (Fig. 3e–f, supplementary fig. S1). The $p75^{NTR}$/TrkB ratio was calculated for the hippocampus in control and GS dams, and remained unaltered (Fig. 3g).

Stress significantly decreased p11 protein concentrations in the DG ($p < 0.05$) and CA1 ($p < 0.01$) of the hippocampus, but not in the CA3 or in the total hippocampus (Fig. 2e–f, 4a). No changes in p11 immunoreactivity were found in the NAc core (Fig. 4b).

Since we found reduced protein levels of BDNF and increased $p75^{NTR}$ immunoreactivity in the hippocampus, we performed a TUNEL staining to see whether early GS leads to increased hippocampal apoptosis in the dams. TUNEL-positive cells were quantified in the CA (CA1 + CA3) and DG, but no significant differences were found between stressed and control dams in any of the analyzed brain regions

Table 1
Analysis of full-term pregnancies, together with measures of litter size at P0 and P28, postnatal survival rate of the pups and gender distribution in the litters. Stress during early gestation negatively affects the odds for full-term pregnancy, although it does not affect litter size. It does not affect survival rate of the pups between P0 and P28 or gender distribution in the litters. Data are shown as mean ± SEM when applicable.

	Full-term pregnancy (%)	Litter size P0 (#)	Litter size P28 (#)	Postnatal survival pups (%)	# male pups P28	# female pups P28	% male pups P28
Control	82.5	6.57 ± 0.58	6.00 ± 0.55	91.51 ± 3.09	3.57 ± 0.60	2.43 ± 0.45	57.24 ± 6.63
Stress	42.2	5.56 ± 0.42	4.94 ± 0.46	90.51 ± 5.44	2.56 ± 0.36	2.38 ± 0.39	50.81 ± 7.15
Statistics	$\chi(1) = 14.465$ $p < 0.001$***	$F(1,28) = 2.059$ n.s. ($p = 0.162$)	$F(1,28) = 2.207$ n.s. ($p = 0.149$)	$F(1,28) = 0.024$ n.s. ($p = 0.879$)	$F(1,28) = 2.020$ n.s. ($p = 0.166$)	$F(1,28) = 0.008$ n.s. ($p = 0.928$)	$F(1,28) = 0.413$ n.s. ($p = 0.526$)

*** indicates significant difference between stressed and control groups with $p < 0.001$ (control $n = 14$, stress $n = 16$).

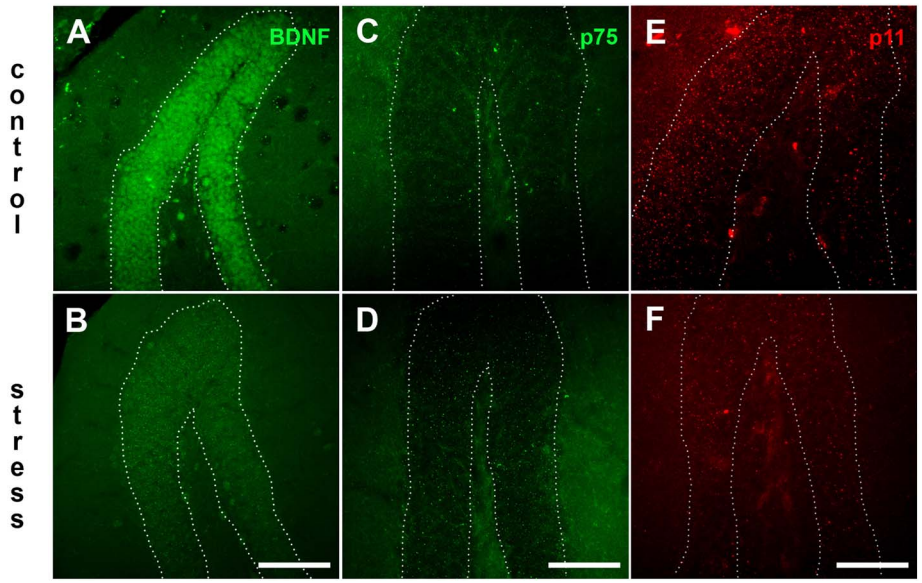

Fig. 2. Immunohistochemical stainings for BDNF, $p75^{NTR}$ and p11 in control (upper panel) and GS (lower panel) dams. Shown are representative photomicrographs of the DG which was immunohistochemically stained for BDNF (a,b), $p75^{NTR}$ (c,d) or p11 (e,f). BDNF staining is visible in the entire soma of the granular DG cells, while $p75^{NTR}$ and p11 vesicular staining is visible as bright spots throughout the DG. GS decreased immunohistochemical staining of BDNF and p11, but increased staining for $p75^{NTR}$. The DG is delineated by a dashed white line. Scale bars represent 200 µm for (a,b) and 100 µm for (c–f).

(Fig. 4c, supplementary fig. S1). Since apoptosis can also decrease the size of brain structures we also measured the surface size of the hippocampus at 6 specific bregmas. No difference in area surface was found in the DG, CA1, CA3 or entire hippocampus (Supplementary table S2).

4. Discussion

GS treatment during pregnancy decreased weight of the dams, increased the chance for spontaneous abortion and increased weight of the offspring at the time of weaning. In the hippocampus of the dam, GS decreased protein levels of BDNF and p11, while it increased $p75^{NTR}$ levels in the hippocampus without affecting TrkB or apoptosis. No changes were found in the NAc core of the dam.

4.1. GS does not affect litter characteristics

Experimental GS is generally achieved by applying restraint stress to the pregnant dam three times daily for 45 min over a period of approximately 7 days. In accordance with the majority of other comparable studies, we did not find effects of GS on litter size, sex distribution or postnatal survival rates of the pups (Pawluski et al., 2011; J. W. Smith et al., 2004; Van den Hove et al., 2005; Van den Hove et al., 2008; van den Hove et al., 2011; Van den Hove et al., 2013; Van den Hove et al., 2006; Yeh et al., 2012). However, a few studies reported increased postweaning mortality and decreased litter size following GS (Baker et al., 2008; van den Hove et al., 2011). These differences can be explained by a different behavioral protocol, with restraint stress being applied during the last week of gestation instead of during the first week.

4.2. GS decreases weight of the pregnant dam but increases weight of the offspring

GS greatly affects body weight of the dam and its offspring. Yet, the timing and procedure of the stress paradigm has a big impact on the outcome which makes direct comparisons between studies difficult. We found an increased weight in early GS pups at weaning (P28), which could not be explained by decreased litter size since litter size and weight at P28 did not correlate. It is known that GS can lead to fetal programming, which increases the risk for obesity in later life (see (Stout et al., 2015) for an overview). Indeed, multiple studies have shown an increased risk for obesity in children of mothers exposed to a natural disaster during pregnancy (Dancause et al., 2012; Dancause et al., 2015; Liu et al., 2016). These results are further supported by a meta-analysis linking gestational stress to an increased obesity risk in children (Tate et al., 2015). Furthermore, maternal salivary cortisol levels during pregnancy were found to be positively associated with overweight children (Hohwu et al., 2015). Not only weight of the offspring, but also weight gain in the pregnant dam is influenced by exposure to stressors. Generally, a decrease in weight gain in dams during gestation and postpartum is reported when rats are exposed to midterm or late GS, which is in agreement with our findings in mice (Baker et al., 2008; Darnaudery et al., 2004; van den Hove et al., 2011; Van den Hove et al., 2013; Van den Hove et al., 2006). Again, a few studies oppose these data since it has also been reported that weight gain remains unaffected by midterm or late GS (Pawluski et al., 2011; Van den Hove et al., 2005; Van den Hove et al., 2008).

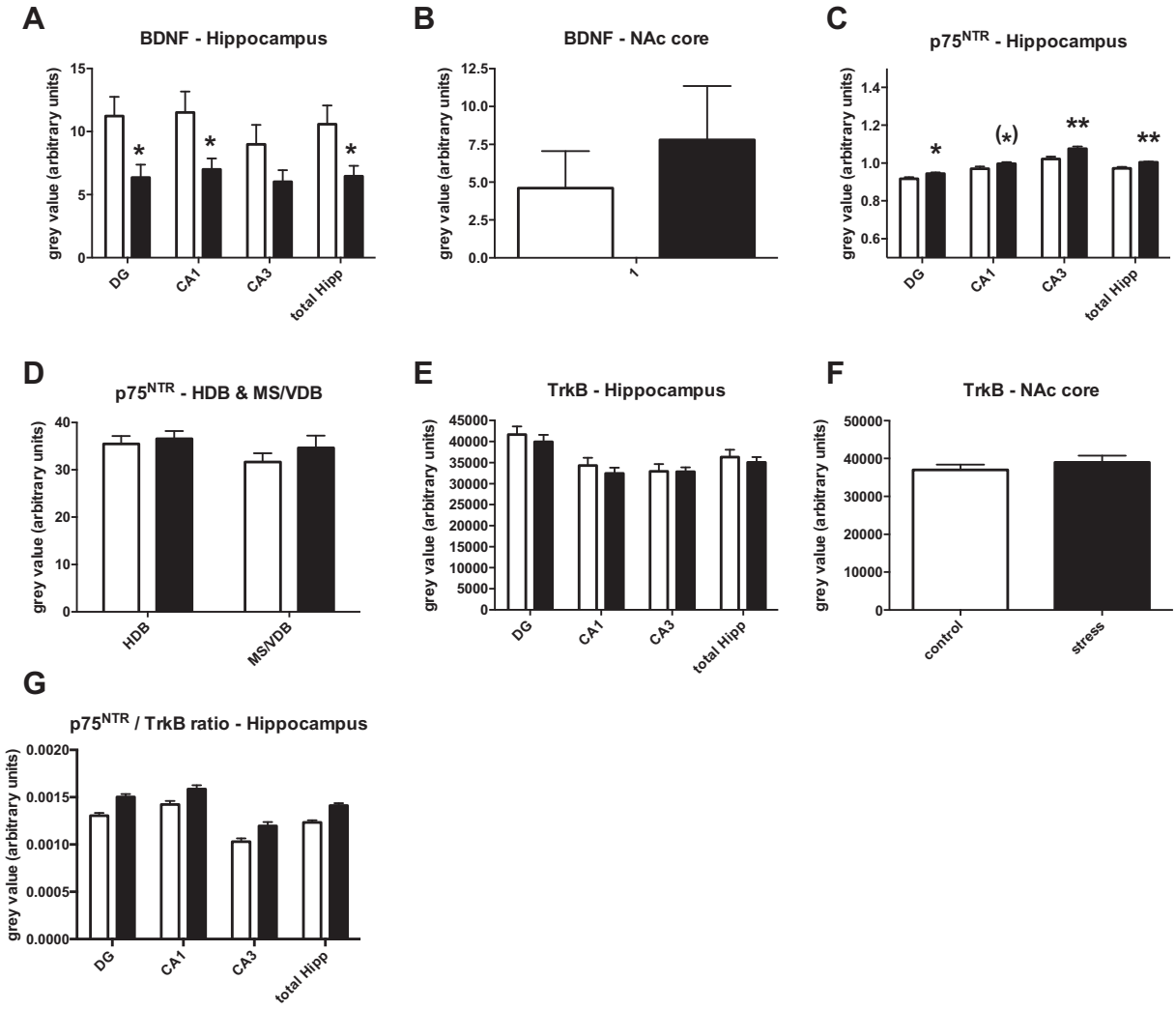

Fig. 3. Immunohistochemical analysis of BDNF (a,b), and its receptors p75^{NTR} (c,d) and TrkB (e,f), and the receptor ratio (g) in the brain of controls (white bars) or GS dams (black bars). Data are shown as mean value + SEM (n = 6 for TrkB and the p75^{NTR}/TrkB ratio, n = 9 for BDNF and p75^{NTR}). (a–b) Stress during early gestation decreases BDNF levels in the DG, CA3 and total hippocampus without altering BDNF levels in the NAc core. (c–d) Stress during early gestation decreases p75^{NTR} levels in the DG, CA3 and total hippocampus without altering p75^{NTR} levels in the MS/VDB or HDB. (e–f) TrkB levels are unaffected in the hippocampus or NAc core by stress. (g) The p75^{NTR}/TrkB ratio remained unchanged. DG = dentate gyrus, CA = cornu ammonis, hipp = hippocampus, NAc = nucleus accumbens, MS = medial septum, HDB/VDB = horizontal/vertical diagonal band of Broca
(*) $0.05 < p < 0.1$; *$p < 0.05$; **$p < 0.01$.

4.3. GS decreases hippocampal BDNF protein levels

Both physical and social stressors are known to disrupt normal BDNF levels in the hippocampus and NAc. While chronic exposure to stressors, such as restraint stress, forced swimming stress, early maternal separation, chronic mild stress, chronic unpredictable stress and psychological stress, generally decreases BDNF mRNA expression and protein levels in the hippocampus (De De Vry et al., 2012; Murakami et al., 2005; Rasmusson et al., 2002; Roceri et al., 2002; Shi et al., 2010; M. A. Smith et al., 1995; Taliaz et al., 2011), it seems that acute stressors increase hippocampal BDNF levels (Marmigere et al., 2003; Shi et al., 2010). In our study, pregnant dams were chronically exposed to GS and showed decreased BDNF protein levels in the DG and CA3 of the hippocampus 28 days after delivery. These subregions were also subject to neurotrophic changes in similar studies (Murakami et al., 2005; Sierksma et al., 2012). It has been postulated that increased BDNF levels following acute stress exposure promotes plasticity as a coping strategy to handle environmental challenges. This mechanism might be disrupted when a chronic stressor exceeds the adaptive capacity of the organism (Marmigere et al., 2003).

A different picture emerges when we look at the VTA-NAc. Mice susceptible to social defeat stress exhibit increased BDNF protein levels in the NAc core, similar to what was found in suicide victims (Berton et al., 2006; Krishnan et al., 2007; Miczek et al., 2011). Chronic mild stress in rats increases BDNF expression in the NAc and causes hypertrophy of medium spiny neurons in the NAc (Bessa et al., 2013). Likewise, BDNF protein levels in the VTA increase when rats are episodically exposed to social defeat stress (Miczek et al., 2011). However, continuous exposure of rats to social defeat over 5 weeks decreases BDNF protein immunolabeling in the VTA (Miczek et al., 2011). This shows that, like in the hippocampus, duration and type of stressor greatly affects BDNF homeostasis in the VTA-NAc. Indeed, a single defeat experience did not affect excitability of dopaminergic VTA neurons, suggesting that an increased excitability and activity-dependent BDNF release into the NAc may be specific for chronic social defeat (Krishnan et al., 2008). Likewise, immunoreactivity for BDNF in the NAc core was unaffected by GS in our study.

4.4. GS increases p75^{NTR} protein levels in the hippocampus without affecting TrkB

TrkB is abundantly expressed in the hippocampus while few p75^{NTR}-

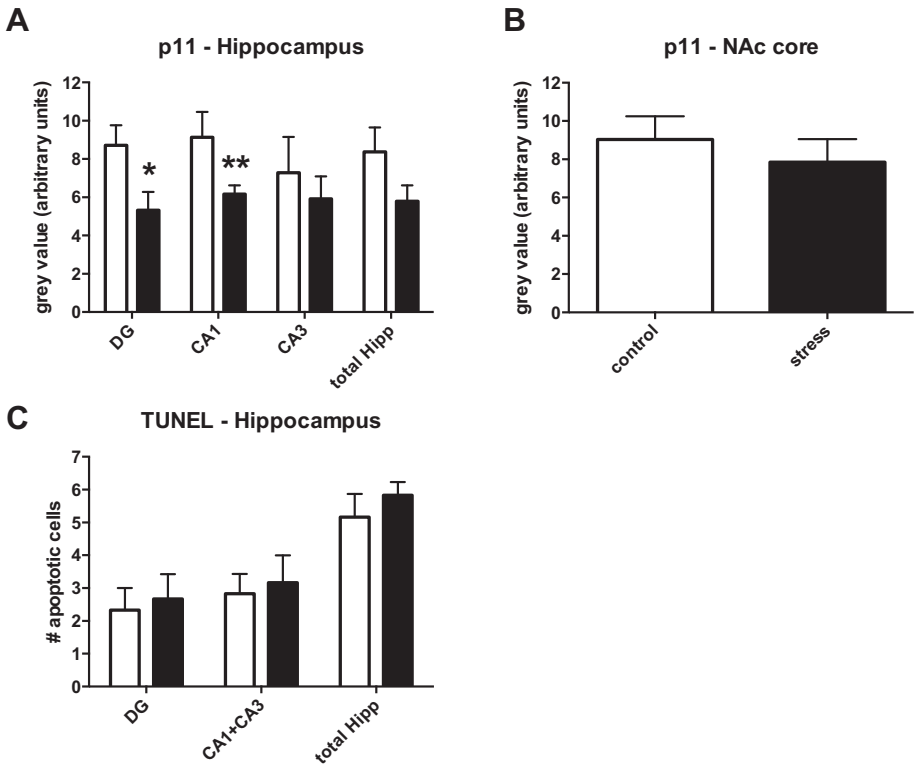

Fig. 4. Immunohistochemical analysis of p11 (a,b) and apoptosis (TUNEL, c) in the brain of controls (white bars) or GS dams (black bars). Data are shown as mean value + SEM (n = 6). (a–b) p11 protein levels are significantly reduced in the DG and CA1 of the hippocampus, but not in the NAc core. (c) No effects of stress during gestation on hippocampal apoptosis were found in the dams. DG = dentate gyrus, CA = cornu ammonis, hipp = hippocampus, NAc = nucleus accumbens $^{*}p < 0.05$; $^{**}p < 0.01$.

positive fibers originating in the medial septum can be found in the hippocampal formation (Barrett et al., 2005; Yan et al., 1997). TrkB is also expressed in the NAc, but at relatively low concentrations compared to the hippocampus (De Vry et al., 2016; Freeman et al., 2003; Yan et al., 1997). Regional expression patterns of these BDNF receptors could therefore contribute to the region-dependent actions of BDNF (Martinowich et al., 2007). Different kinds of stressors can alter the expression and activation of TrkB and $p75^{NTR}$, but the direction of these changes is region-specific and heavily depends on the duration and type of stressor. Chronic forced swim stress and unpredictable mild stress in rats increase hippocampal TrkB expression (Shao et al., 2010; Shi et al., 2010). In contrast, no effects of early GS on hippocampal TrkB levels were found in adult offspring of APPswe/PS1dE9 mice (Sierksma et al., 2012). In addition, mice susceptible to social defeat show no differences in TrkB phosphorylation or in total protein levels in the NAc (Krishnan et al., 2007). Likewise, we found that GS did not affect TrkB protein levels or the $p75^{NTR}$/TrkB ratio in the NAc core or hippocampus. Discrepancies in these findings may be partly attributed to different species and stress paradigms that were studied. When immobilization stress in rats is only applied acutely, hippocampal TrkB expression does not change (M. A. Smith et al., 1995), but its phosphorylation increases greatly (Neeley et al., 2011). This acute effect may be due to a direct interaction between glucocorticoids and TrkB, leading to neuroprotective effects, as has been shown in vivo and in vitro (Jeanneteau et al., 2008). It remains to be studied whether GS can affect TrkB phosphorylation.

$p75^{NTR}$ was abundantly present in the HDB and MS/VDB, but was unaffected by GS in these brain regions. $p75^{NTR}$-positive fibers, originating from the basal forebrain innervate the hippocampal formation. We found that GS increased $p75^{NTR}$-immunolabeling in the hippocampus, especially in the DG and CA3. This is in line with the general view that many different types of insults and cellular stressors, including oxidative stress, seizures and injury, are potent inducers of $p75^{NTR}$ expression (see (Ibanez and Simi, 2012) for an overview). In contrast, no effects of prenatal stress on hippocampal $p75^{NTR}$ were observed in the offspring of APPswe/PS1dE9 mice (Sierksma et al., 2012). $p75^{NTR}$ is also a potent modulator of Trk receptor signaling, functioning as a co-receptor with Trk receptors to create binding sites with higher affinity and specificity for neurotrophins (Esposito et al., 2001). Rather than inducing apoptosis, it can be hypothesized that increases in $p75^{NTR}$ expression following GS, counteract an initial loss in BDNF-TrkB signaling by creating binding sites with higher affinity, without affecting the $p75^{NTR}$/TrkB ratio.

4.5. p11 protein levels decrease in the hippocampus following GS

P11 protein levels paralleled those of BDNF, with decreased levels of both proteins in the hippocampus following GS. No changes in p11 or BDNF immunoreactivity were found in the NAc core. P11 is known to bind to BAD, thereby preventing the inhibition of the anti-apoptotic protein Bcl-2 (Hsu et al., 1997). Therefore, a decrease in hippocampal p11 protein levels, together with a local increase in $p75^{NTR}$ protein, may induce apoptosis in the brain. However, this was not the case in our study, possibly due to compensatory mechanisms via other neuroprotective signaling cascades to cope with the stress and to avoid apoptosis. Stress resilience is known to have a neurobiological basis that involves many different mechanisms (Franklin et al., 2012; Isingrini et al., 2016; Van den Hove et al., 2013), and it is not unlikely that a stress-resilient population may be more capable of efficiently avoiding stress-induced apoptosis. Indeed, 82.5% of the dams with a vaginal plug in the control group successfully delivered offspring, in contrast to a mere 42.2% of the stressed dams. Since only dams that successfully delivered offspring were included in the immunohistochemical analysis, the results may reflect a stress-resilient group compared to the aborting dams. It is also possible that apoptotic cells may have been cleared by the time the animals were sacrificed, which was 5 weeks after stress exposure. Nevertheless, the hippocampal volume was not affected by the GS paradigm as determined by recurrent area surface analyses. Albeit beyond the scope of our research question, it could be expected that non-resilient, aborting dams are even more vulnerable to gestational stress, and thereby more changes can be expected in hippocampal neurotrophic signaling.

5. Conclusions

This study shows that GS has a negative impact on pregnancy in mice. In addition, stress during pregnancy negatively affects the neurotrophic system in the hippocampus of the dams, and thereby reduces hippocampal plasticity. Of note, only dams that successfully delivered pups were included in the weight gain and immunohistochemical analyses. Hence, results from this study may reflect a resilient population only. Susceptible mice with aborted pregnancies may feature more severe changes in neurotrophic signaling and these effects could have been excluded from our results by the experimental design. Nevertheless, as no changes in the neurotrophic system were observed in the NAc core, this indicates that the hippocampus is more sensitive to GS.

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Declaration of interest

Each of the authors declares no conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the work submitted that could inappropriately influence, or be perceived to influence his work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mcn.2018.02.009.

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