C1

Hippocampal free corticosterone levels show an ultradian rhythm in Wistar rats

S.K. Droste, L. de Groote, H.C. Atkinson, S.L. Lightman, J.M. Reul and A.C. Linthorst

Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Bristol, UK

Plasma corticosterone levels in rodents are characterised by a diurnal rhythm with low levels in the morning and markedly higher levels towards the evening, the activity phase of these nocturnal animals. Apart from diurnal changes, plasma corticosterone levels also display an ultradian rhythm [1], possibly resulting from its pulsatile secretion by the adrenal cortex [2]. At present it is unknown whether this ultradian rhythm in glucocorticoid hormone persists across the blood-brain barrier and can be found in the extracellular space of the brain. To clarify this issue, we designed a series of *in vivo* microdialysis studies to measure corticosterone levels in the rat hippocampus, a principal site of glucocorticoid action in the brain. Importantly, because the extracellular fluid is devoid of corticosterone binding proteins, dialysate levels represent the free, i.e. the biologically active fraction, of this glucocorticoid [3].

Male and female Wistar rats were equipped with a guide cannula under isoflurane anaesthesia. Seven days later a microdialysis probe was inserted, under isoflurane anaesthesia, into the hippocampus. After 2 days, collection of dialysate samples was started at 05:00 h and continued for 48 h. Sample intervals were 10 min or 30 min between 08:00-22:00 h and 22:00-08:00 h, respectively. On the second day animals were subjected to novelty (30 min) or swim stress (15 min, 25°C), or left undisturbed in their home cage. A sensitive radioimmunoassay was used to measure dialysate corticosterone. Data were analysed using Pulsar PC and SPSS software.

It was found that hippocampal free corticosterone levels show a clear pulsatile pattern in both male and female rats. Interestingly, in both sexes the pulse amplitude increased towards the evening. A comparison between male (n=15) and female (n=10) rats over a 12 h period (09:00-21:00 h), revealed no significant gender differences ($P > 0.05$, Student's t test) in the total number of pulses (male (m): 14.6±0.5 vs. female (f): 14.5±1.2 pulses) and the pulse amplitude (0.11±0.01 (m) vs. 0.09±0.01 (f) μg/dl). Moreover, the mean corticosterone level was similar in male and female rats (0.14±0.02 (m) vs. 0.11±0.01 (f) μg/dl). While both novelty and swim stress caused a rise in free corticosterone in male and female rats, the ultradian rhythm was rapidly restored after termination of the stressors (maximal effect in male rats: novelty: 0.27±0.08 μg/dl, swim: 0.79±0.34 μg/dl; female rats: novelty 0.27±0.05 μg/dl, swim: 1.27±0.33 μg/dl).

These data demonstrate for the first time the existence of an ultradian rhythm of free corticosterone in the hippocampus of rats. Such an ultradian pattern of hormone levels could be of great significance for glucocorticoid action in the hippocampus during ongoing conditions and for the role of this brain structure in the regulation of the hypothalamic-pituitary-adrenal axis and other glucocorticoid-sensitive systems over the diurnal cycle.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

C2

Rapid turnover of nuclear glucocorticoid receptors in the rat hippocampus after pulsatile corticosterone administration

B.L. Conway-Campbell, M.A. McKenna, H.C. Atkinson, C.C. Wiles, S.A. Wood, L.R. Harrison, E.S. Castrique and S.L. Lightman

Department of Medicine,, Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Bristol, UK

Glucocorticoids (GCs) act via intracellular receptors which translocate into the nucleus to regulate target genes. There are two types of GC receptors, the high affinity mineralocorticoid receptor (MR) and the low affinity glucocorticoid receptor (GR). The secretion of GCs occurs in distinct pulses depending on numerous physiological factors (Atkinson et al. 2006); however, the functional significance of this pulsatility is unknown. Here, we present two models of corticosterone (cort) presentation in the rat: IP injection to mimic the prolonged cort release of a stress response and IV injection to mimic basal pulsatility. This study aims to determine how different patterns of cort presentation affect GR and MR activity in the hippocampus (HC), an important site for stress-related memory and learning.

Male Sprague-Dawley rats (n=6/group) were anaesthetised with IM injection of Hypnorm (fentanyl citrate 0.252 mg/kg and fluanisone 8 mg/kg) after IP injection of Diazepam (4 mg/kg) then subjected to bilateral adrenalectomy and jugular cannulation (IV). After recovery for 5 days, each was given either 1 bolus IP injection (750 μg cort) or 2 bolus IV injections (100 μg cort) at times 0 and 120 min. Animals were killed at times 0, 10, 15, 30, 60 and 120 min. The HC was rapidly dissected and frozen. Nuclear extracts were prepared and analysed by Western blot with GR or MR antibodies to determine nuclear GR and MR levels.

IP injection caused prolonged high plasma cort levels (466±164 ng/ml at 30 min, 206±31 ng/ml at 60 min) decreasing by 120 min (38±13 ng/ml). Nuclear translocation of both GR and MR in the HC was prolonged (21±4-fold GR, 23±5-fold MR at 30 min, and 14±4-fold GR, 31±5-fold MR at 60 min).

IV injection caused a rapid pulse of GC (883±157 ng/ml) at 1 min. This was rapidly cleared as the half life of cort in blood is 10 min. Nuclear translocation of both GR and MR was observed in the HC at 10 min (19±6-fold GR, 14±3-fold MR) reaching a maximum at 15 min (22±9-fold GR, 19±4-fold MR). The retention time of GR in the nucleus was much shorter in duration than that observed after the IP injection. The depletion of nuclear GR after each pulse was evident by 30 min (9±2-fold) returning to near basal levels by 60 min. MR displayed a much slower nuclear depletion with high nuclear levels of MR throughout the time course decreasing only at 120 min after each pulse.

Cort IP injection provides a model of a stress-like prolonged presence of GR and MR in HC nuclei as described by Kitchener et al. (2004). IV injection provides a temporal model of basal pulsatility with rapid turnover of GR but not MR in HC nuclei. Our findings have significant implications for GR as a sensitive mediator of adrenal GC pulses transmitted to the HC. The highly fluctuating nature of nuclear GR levels (but not MR levels) may be functionally important in allowing dynamic interactions with physiological responses e.g. stressors.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

C3

The role of the vasopressin V1b receptor in the HPA axis response to acute stress: molecular and pharmacological studies

J. Roper[1], A. O'Carroll[1], E.J. Grant[2] and S.J. Lolait[1]

[1]University Of Bristol, Bristol, UK and [2]Department of Molecular Pharmacology, Organon Laboratories Ltd, Newhouse, UK

Vasopressin (VP) is the hormonal regulator of water homeostasis and has major effects on behaviour and vascular tone. In addition to this it is also a key regulator of the hypothalamic-pituitary-adrenal (HPA) axis, an action mediated through the G protein-coupled V1b receptor (R) (or V3R) predominantly found on the corticotrophs of the anterior pituitary. Although corticotrophin releasing hormone (CRH) seems to be the dominant adrenocorticotrophin (ACTH) secretagogue in rodents in response to acute stress (e.g. restraint), VP synergizes with CRH in activating the release of ACTH and may be preferentially released in response to some acute stressors (e.g. insulin-induced hypoglycaemia (1,2)). To further investigate the role of the VP V1bR in the HPA axis response to stress, we compared the effects of a recently described V1bR antagonist (Org 52186 (3)) on the levels of plasma ACTH and corticosterone (CORT) in V1bR knockout mice subjected to acute restraint stress. Org 52186 is a potent antagonist at the human V1bR and exhibits >1000-fold selectivity over the closely related V1a, V2 or oxytocin receptors. Adult male and female V1bR KO mice (and wild-type littermates) were administered s.c. with vehicle or Org 52186 (10 or 30mg/kg) 2h prior to acute restraint stress (30min in a 50ml 'Falcon' tube). Both doses of the V1bR antagonist significantly reduced stress-induced plasma ACTH and CORT levels in wild-type mice (ACTH: male wild-type restraint 129±16pg/ml, n=4, vs male wild-type restraint + Org52186 (30mg/kg) 45±7.87pg/ml, n=5; $p<0.05$). The HPA axis response to restraint was decreased in the V1bR KO (ACTH: male wild-type restraint 129±16pg/ml, n=4, vs male knockout + restraint 63±14pg/ml, n=5; $p<0.001$ - pretreatment with Org 52186 did not significantly effect the stress-induced hormone levels in these mice. Similar results were obtained in the female knockout and wild-type mice (e.g. vehicle + restraint 73±8pg/ml, n=7, vs Org 52186 (30mg/kg) + restraint 21±5.6pg/ml, n=6; $p<0.001$). In contrast to some previous studies on the VP-deficient Brattleboro rat (4), our studies clearly demonstrate that the V1bR is important for a normal acute restraint stress-induced ACTH and CORT response, and suggest that it is unlikely that possible compensatory/developmental changes resulting from the ablation of the V1bR gene play an important role in the HPA axis response to acute restraint in the V1bR KO.

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Paulmyer-Lacroix O *et al.* (1994). *M J Mol Endocrinol* **13**, 313-320.

Org52186 Patent no. WO/2006/095014; 2-(4-0X0-4H-QUINAZ0LIN-3-YL) Acetamides and their use as Vasopressin V3 antagonists.

Zelena D *et al.* (2004). *Brain Research Bulletin* **63**, 521-530.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

C4

Central vasopressin mechanisms contribute to the mediation of the cardiovascular response to stress

N. Japundzic-Zigon[1], S. Stojičić[2], S. Milutinović[1], O. Šarenac[1], S. Milosavljević[1], J.F.R. Paton[3] and D. Murphy[4]

[1]Pharmacology, School of Medicine University of Belgrade, Belgrade, Serbia, Yugoslavia, [2]Conservative Dentistry and Endodontics, School of Dentistry, Belgrade, Serbia, Yugoslavia, [3]Physiology, Bristol Heart Institute, School of Medical Sciences, University of Bristol, Bristol BS8 1TD, UK and [4]The Molecular Neuroendocrinology Research Group, Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Bristol BS1 3NY, UK

Emotional stress may contribute to the development of hypertension. However, the central mechanisms involved in the mediation of the cardiovascular response to emotional stress have not been fully investigated [1]. With the latest discovery of a new vasopressin V1b antagonist with potent anxiolytic activity [2], we were prompted to investigate the contribution of central vasopressin mechanisms in the cardiovascular response to emotional stress. Experiments were performed in conscious rats equipped with left lateral intracerebroventricular (icv) cannula (under 0.4 ml, 10% ketamine plus 0.1 ml, 2% xylazine, i.p. anesthesia) for drug injection and left femoral arterial catheter (under 4% concentration percentage for induction and 2% for maintenance of halothane anesthesia) for arterial pressure recording. Equidistant sampling allowed direct spectral analysis (fast Fourier transform) of SBP and HR in very low (VLF: 0-0.2Hz), low (LF: 0.2-0.8Hz) and high frequency (HF: 0.8-3Hz) domains. Rats were submitted to two models of stress: air-jet (by blowing air into the nose of a rat for 2 min, n=6) and immobilization (by covering rat with Plexiglas restrainer for 15 min, n=6). Air-jet induced a sharp rise in SBP (168±3mmHg, $p<0.01$) and HR (525±10bpm, $p<0.01$) and gradual recovery with appearance of sympathetically mediated LF BP variability. V1a (SR49059, 100ng, 500ng, icv) and V1b (SSR149415, 100ng, 500ng, icv) antagonists (n=6/each group) did not modify basal values but did reduce the increase of the area under the SBP curve (sum of SBP values, $3.6x10^5$±0.1mmHg, $p<0.05$ in nontreated rats,

$3.3x10^5$±0.2mmHg, p>0.05 in 100ng V1a PT rats, $3.4x10^5$±0.2mmHg, p>0.05 in 500ng V1a PT rats, $3.2x10^5$±0.2mmHg, p>0.05 in 100ng V1b PT rats and $3.3x10^5$±0.1mmHg, p>0.05 in 500ng V1b PT rats), the increase of HRmax (488±10bpm, p<0.05 and 469±14bpm, p<0.05, respectively) during exposure to air-jet and shortened the recovery period of SBP (361±22s in nontreated rats, 206±46s, p<0.001 in 100ng V1a PT rats, 113±15s, p<0.001 in 500ng V1a PT rats, 138±42s, p<0.001 in 100ng V1b PT rats, and 60±8s, p<0.001 in 500ng V1b PT rats) and HR (378±18s in nontreated rats, 216±43s, p<0.05 in 100ng V1a PT rats, 138±21s, p<0.001 in 500ng V1a PT rats, 175±57s, p<0.001 in 100ng V1b PT rats and 140±26s, p<0.001 in 500ng V1b PT rats) and prevented the appearance of LF-SBP. The V1b also reduced the SBPmax increase during exposure to stress (145±9mmHg, p<0.05 in 100ng V1b PT rats and 151±5mmHg, p<0.05 in 500ng V1b PT rats). Immobilization induced a rise of SBP (153±4mmHg, p<0.01), LF-SBP and respiratory-related HF-SBP variability; it did not affect HR but did enhance the vagally mediated HF-HR variability. Both V1a and V1b (n=6/each group) reduced the evoked increases in SBP and SBP variability during immobilization. The V1a PT rats submitted to immobilization now exhibited significant tachycardia (495±65bpm, p<0.05) and failed to increase HF-HR variability. The results suggest that both vasopressin V1a and V1b receptors are involved in the central mediation of the cardiovascular response of rats exposed to emotional stress.

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C5

Hippocampal neurogenesis in the prenatal stress rat is enhanced by agomelatine treatment. Functional implications for anxiety behaviour

S. Morley-Fletcher[1], J. Mairesse[1], O. Viltart[1], A. Daszuta[2], A. Soumier[2], M. Banasr[2], A. Zuena[3], P. Casolini[3], E. Mocaer[4] and S. Maccari[1]

[1]Lab. of Perinatal Stress, University of Lille 1, Villeneuve d'Ascq, France, [2]2 IC2N, CNRS, Marseille, France, [3]University of Rome La Sapienza, Rome, Italy and [4]IRIS, Courbevoie, France

Prenatal stress (PS) in the rat is a well documented model of early stress that has high face and predictive validity as animal model of depression (Maccari et al. 2003; Morley-Fletcher et al. 2004). Indeed, PS rats present a life span reduction of hippocampal neurogenesis (Lemaire et al. 2000), increased anxiety and impairment of the feedback inhibition of the hypothalamus-pituitary adrenal axis. We here evaluated the effect of a chronic treatment (6 weeks, 40 mg/kg i.p. daily) with the new antidepressant agomelatine, a melatonin agonist with 5-HT2C antagonist properties, on hippocampal neurogenesis in PS male adult rats and, on PSA-NCAM expression, a marker of neuroplasticity. To investigate also the functional, behavioural impact of neurogenesis, we tested animals in the elevated-plus maze test to assess their anxiety-like response. To evidence neurogenesis and cell survival, the thymidine-analogue bromodeoxyuridine (BrdU, 75 mg/kg i.p. twice daily for 4 days) was injected after 3 weeks of the agomelatine treatment which was then continued for an additional 3 weeks. The results indicate a markedly reduced neurogenesis in the dentate gyrus of PS rats and an enhanced PSA-NCAM expression (ANOVA, group by treatment interaction, $F(1,21) = 10.53$, $P < 0.01$). The effects of PS were reversed by the chronic agomelatine treatment Agomelatine's effect on survival was selectively observed in the ventral part of the dentate gyrus (ANOVA region by group by treatment interaction, $F(1,26) = 4.73$, $P < 0.05$), a brain region specifically involved in anxiety (Kjesltrup et al. 2002). Moreover in PS animals agomelatine did not modify the ratio between neurons and glial cells assessed by NeuN and GFAP labelling. Behaviourally, PS rats treated with agomelatine spent more time on the open arms of the elevated plus maze, (ANOVA, group by treatment interaction, $F(1,27) = 7.06$, $P < 0.05$) suggesting a possible causal link between increased hippocampal neurogenesis and attenuated anxiety-like behaviour in a validated model of depression. The results obtained with agomelatine provide further evidence of neuroplasticity as one of the targets of antidepressants and further reinforce the high predictive validity of the PS rat as animal model of depression.

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Morley-Fletcher S, Darnaudery M, Mocaer E, Froger N, Lanfumey L, Laviola G et al. (2004). Neuropharmacology 47, 841-847.

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C6

Differences in subregion-specific translocation patterns of mineralocorticoid and glucocorticoid receptors in rat hippocampus revealed by immunohistochemistry

R.A. Sarabdjitsingh, O. Meijer and R. de Kloet

Department of Medical Pharmacology, LACDR, University of Leiden, Leiden, Netherlands

Activation of glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) by corticosteroids results in nuclear translocation of the receptor-ligand complex. There, the receptors can bind to DNA for transcriptional regulation. Though this cellular mechanism is well established in cell lines, very little is known about the subcellar behaviour of the receptors in the brain and the associated consequences for DNA binding and gene expression. The aim of this study was to examine the translocation patterns of MR and GR in the different subfields of the rat hippocampus in detail by using immunohistochemistry and confocal imaging. Based on studies that have described differences in receptor expression pattern in the hippocampus and affinities for corticosterone, we hypothesize (1) differences in translocation patterns for the different hippocampal subregions and (2) different translocation speed for MR and GR within one area.

Here, we present data on the translocation of MR and GR in hippocampal subregions CA1, CA2, CA3 and dentate gyrus after a single high corticosterone pulse. In order to prevent translocation induced by endogenously synthesized corticosterone, adrenalectomised male Sprague-Dawley rats (n=3) were terminally anaesthetised at 0, 30, 60, or 120 min after i.p. 3 mg/kg corticosterone complexed to HBC to increase solubility. Animals were anesthetized using 0.4 l/min isoflurane intra-nasally. Primary antibodies for MR (MR 1D5 1-18, Gomez-Sanchez et al. 2005) and GR (H300, Santa Cruz Biotechnology) were used for immunofluorescence and confocal microscopy to visualize and quantify the subcellular distribution of the receptors.
Results indicate (1) large subregion-specific differences in translocation patterns and (2) different behaviours for MR and GR within areas. Indeed, a strong increase in nuclear immunoreactivity for both GR and MR was observed in CA1 ($p<0.001$ vs. $p<0.01$) and CA2 ($p<0.01$ vs NS) after corticosterone administration. Interestingly, in the DG, a markedly increase was only observed for nuclear GR ($p<0.05$) while nuclear MR did not change after steroid treatment. The results of this study suggest a revision of the view that MR and GR uniformly translocate to the nucleus upon corticosterone administration. Even though the consequences of this differential translocation in the hippocampus on gene expression and function have to be investigated in more detail, the data suggest that for MR mediated effects ligand availability is more of a limiting factor in the CA1 area, while in other hippocampal subfields the MR signal may be modulated primarily by receptor number or posttranslational modifications. The next step is to study these region-specific translocation patterns of MR and GR in a relevant physiological context, like the ultradian release of corticosterone.
Gomez-Sanchez CE et al. (2006). Endocrinology 147, 1343-1348.

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C7

Opioids and suppressed hypothalamo-pituitary-adrenal (HPA) axis responses in late pregnant rats to central neuropeptides signalling metabolic state

J. Bales, P.J. Brunton and J.A. Russell

Edinburgh University, Edinburgh, UK

In pregnancy metabolic actions of stress-stimulated glucocorticoids may compromise energy supply to the fetuses. I.C.V. injection of orexin-A or neuropeptide Y (NPY), signalling energy lack, stimulates the HPA axis in virgin but not late pregnant rats [1,2]. Here we studied responses to I.C.V. ghrelin, which acts like orexin via NPY neurones, and to insulin-induced hypoglycaemia (IIH). We tested roles of endogenous opioid [3] in suppressing responses to NPY and orexin. Rats (n=5-7/group) were implanted (halothane anaesthesia) 5 days before experiment (pregnancy day 21) with a jugular vein cannula, and an I.C.V. cannula if required for 2 µl aCSF ± peptide injections. Rats were housed singly, in standard conditions (lights on 07.00h, off 19.00h), and cannulae connected *ca* 07.30h, 2h before experiment. Blood samples (replaced by 0.9% saline) were taken for ACTH and corticosterone assay pre- and post-treatment; 240 or 90 min later brains were collected after decapitation or formaldehyde fixation-perfusion (pentobarbitone anaesthesia, 42 mg/kg I.P.), for quantitative in situ hybridisation or Fos immunocytochemistry on coronal cryostat or frozen sections, respectively. Data were analysed by ANOVA. In virgins I.C.V. ghrelin (2 nmol) increased plasma ACTH and corticosterone concentrations by 38% and 65%, respectively (at 10-30 min, n=6, $p<0.05$), but had no significant effects in late pregnant rats; similarly, ghrelin increased parvocellular paraventricular nucleus (pPVN) Fos expression (3.9x, $p<0.05$) only in virgins. As expected, NPY (1 nmol I.C.V.) alone only activated the HPA axis in virgins (increased plasma ACTH, pPVN CRH and vasopressin (VP) mRNA [see 2] and Fos (3.5x) expression). Naloxone (5 mg/kg I.V.) had no effect in virgins, but after naloxone in pregnant rats, NPY increased plasma ACTH 2.7x at 15 min, pPVN CRH and VP mRNA expression 1.6x and 15.2x, and Fos counts by 2.3x (all $p<0.05$). I.C.V. orexin-A (1.4 nmol) increased pPVN Fos counts (2.1x) and plasma ACTH (1.9x at 15 min; both $p<0.05$) only in virgins [1]. Naloxone had no effects in virgins, but in pregnant rats it restored orexin responses: increased plasma ACTH (1.6x, $p<0.05$), and increases in CRH and VP mRNA expression in the pPVN (2.2x and 5.5x vs. orexin alone, respectively, $p<0.05$). Thus endogenous opioid suppresses actions of NPY, and hence of orexin, and maybe ghrelin (since it acts via NPY), on the HPA axis in late pregnancy. In contrast, IIH induced by I.V. insulin injection (10 U/kg) in virgin and pregnant rats similarly reduced blood glucose (to ca 2 mmol/l), increased plasma ACTH (by, mean±s.e.m., 46.1±17.8 and 35.6±7.8 pg/ml) and pPVN VP mRNA expression (by 3.3x and 2.3x; all $p<0.05$). Evidently activation of the HPA axis by IIH is intact in late pregnancy, and is does not appear to be mediated by NPY, orexin or ghrelin.
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C8

Maternal stress alters endocrine function of the feto-placental unit in rats

O. Viltart[1], J. Lesage[1], J. Mairesse[1], C. Breton[1], B. Bréant[2], T. Hahn[3], M. Darnaudéry[1], S.L. Dickson[4], J. Seckl[5], C. Vanbesien-Mailliot[1], J. M. Reul[6], D. Vieau[1] and S. Maccari[1]

[1]Dept Adaptative Neuroscience and Physiology, University of Lille 1, Villeneuve d'Ascq, France, [2]INSERM U671, Paris, France, [3]Institute of Histology and Embryology, University of Graz, Graz, Austria, [4]Dept Physiology/Endocrinology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy of Gothenburg University, Gothenburg, Sweden, [5]Molecular Medicine Centre, Western General Hospital, Edinburgh University, Edinburgh, UK and [6]Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Bristol, UK

Prenatal stress (PS) can cause early and long term developmental effects mainly through altered maternal glucocorticoid status.