Effects of maternal exposure to social stress during pregnancy: consequences for mother and offspring

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Abstract

A suboptimal *in utero* environment, for example, as a result of maternal stress, can have detrimental effects on the pregnancy and long-term adverse ‘programming’ effects on the offspring. This article focuses on the effects of prenatal social stress on the mother, her pregnancy and the offspring, since these issues have ethological relevance in both animals and humans. The consequences of social stress exposure depend on when during pregnancy the stress occurs, and many of the effects on the offspring are sex specific. Social stress during early pregnancy tends to result in pregnancy loss, whereas stress exposure later in pregnancy, when the mother has already invested considerable resources in the foetuses, results in programmed offspring of low birth weight: a risk factor for various adulthood diseases. Neuroendocrine and behavioural responses to stress in the offspring are particularly sensitive to foetal programming by prenatal stress, indicated by enhanced hypothalamo-pituitary-adrenal (HPA) axis responses and increased anxiety behaviour, which result from permanent changes in the offspring’s brain. The dysregulation of HPA axis function may also interfere with other systems, for example, the hypothalamic-pituitary-gonadal axis, as there is evidence for alterations in steroidogenesis, reproductive potential and impaired reproductive/social behaviours in prenatally stressed offspring. Prenatal social stress also programmes future maternal behaviour, highlighting the potential for negative phenotypes to be transmitted to future generations. The possible mechanisms through which maternal stress during pregnancy is transmitted to the foetuses and the foetal brain is programmed by prenatal stress and the potential to overwrite programming of the offspring are discussed.

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Introduction

Adverse early-life experiences, including maternal exposure to stress during pregnancy, can ‘programme’ persistent changes in several physiological systems and behaviours, probably via epigenetic mechanisms (Meaney *et al.* 2007). In rodents, prenatal stress is associated with negative pregnancy outcomes such as low birth weight, reduced litter sizes and lower survival rates (de Catanzaro 1988, Pratt & Lisk 1991, Brunton & Russell 2010, Paris *et al.* 2011), and in the adult offspring, it is associated with heightened anxiety (Fride & Weinstock 1988, Vallee *et al.* 1997, Fan *et al.* 2009, Brunton & Russell 2010), enhanced or prolonged hypothalamo-pituitary-adrenal (HPA) axis (Fig. 1) responses to acute stress (Takahashi & Kalin 1991, Weinstock *et al.* 1992, McCormick *et al.* 1995, Koenig *et al.* 2005, Fan *et al.* 2009, Brunton & Russell 2010), hypertension (Igosheva *et al.* 2004), impaired glucose homeostasis (Brunton *et al.* 2013), insulin resistance (Nilsson *et al.* 2001), diet-induced obesity (Nilsson *et al.* 2001, Tamashiro *et al.* 2009), impaired neural development (Lemaire *et al.* 2000), cognitive deficits

(Lemaire *et al.* 2000, Paris & Frye 2011, Paris *et al.* 2011), and abnormal social (Patin *et al.* 2005, Lee *et al.* 2007) and reproductive behaviours (Holson *et al.* 1995, Frye & Orecki 2002).

These programming effects may be considered to be predictive adaptations that inform the offspring of an unpredictable postnatal environment and permit the foetus to adapt in order to cope with unfavourable conditions (Gluckman & Hanson 2004). For example, enhanced behavioural and neuroendocrine responses to stress may reflect greater vigilance to environmental threats, which may promote survival even if this has a long-term cost (McEwen 2008) that reduces life expectancy (Claessens *et al.* 2011). However, often this programming is maladaptive, particularly when there is a mismatch between the predicted and the actual postnatal environment, and this can increase the susceptibility of the offspring to various diseases, for example, cardiovascular disease, diabetes mellitus type 2, obesity, cognitive decline and mood disorders (Seckl & Holmes 2007).

The majority of studies investigating the effects of prenatal stress on the offspring have been carried

Figure 1 The HPA axis. Stressful stimuli activate neurosecretory corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) neurones located in the parvocellular region of the paraventricular nucleus (pPVN) in the hypothalamus. Upon activation, these neurones release CRH and AVP from their nerve terminals at the median eminence into the hypophyseal portal blood system. CRH and AVP stimulate (+) adrenocorticotrophic hormone (ACTH) release from anterior pituitary corticotrophs and an increase in the expression of the ACTH precursor, pro-opiomelanocortin, mRNA in the anterior pituitary. ACTH in turn stimulates the secretion of glucocorticoids (corticosterone in rats and cortisol in pigs) from the adrenal cortex. Glucocorticoids inhibit their own release by providing negative feedback inhibition (–) via glucocorticoid receptors expressed in the hippocampus, PVN and anterior pituitary and via mineralocorticoid receptors expressed in the hippocampus. 3V, third ventricle.

out in rodents. Multiple paradigms are reported in the literature, such as exposure of pregnant rats, mice or guinea pigs to repeated restraint (Henry *et al.* 1994), immobilisation (Ward & Weisz 1984), noise (Fride & Weinstock 1984), strobe lighting (Kapoor & Matthews 2005), social stress (Bosch *et al.* 2007, Brunton & Russell 2010), electric shocks (Takahashi & Kalin 1991), hypoxia (Fan *et al.* 2009) or chronic variable stress (exposure to a combination of different stressors on an unpredictable basis; Koenig *et al.* 2005, Lee *et al.* 2007, Mueller & Bale 2008), either throughout or during a specific period of gestation.

It can be argued that many of these models are not accurate reflections of the type of stress women are likely to experience during pregnancy, which often have a social basis, for example, bullying, pressure at work/heavy workload, bereavement, intimate partner abuse or social instability/disadvantage (Bjorkqvist 2001, Valladares *et al.* 2009, Lee *et al.* 2011, Katz 2012, Laszlo *et al.* 2013, Mahenge *et al.* 2013); thus, animal models of prenatal stress that involve a social component may provide better insight for translational approaches.

The aim of this article is to review the effects of social stress exposure during pregnancy on the offspring.

The article mainly focuses on rodent models of social stress, but it also considers models in other larger species. Sex differences in the sensitivity to programming are considered, and using evidence from other models of prenatal stress, what is known about the mechanisms involved is discussed. Finally, the possible mechanisms through which maternal stress exposure is transmitted to the foetus and the possibility of reversing the detrimental effects of foetal programming are explored.

Animal models of social stress during pregnancy

Rodent model of prenatal social stress

Several animal models of social stress have been devised, including social isolation and overcrowding; however, the resident–intruder paradigm is probably the most commonly utilised one (Blanchard *et al.* 2001). In this model, an ‘intruder’ is transferred into the home cage of a ‘resident’ (usually a same-sex unfamiliar conspecific) for a specified period of time. This is generally carried out using male rodents and results in the resident being aggressive towards the intruder, which exhibits submissive behaviour. Females are typically less aggressive than males, with the exception of the first half of the lactation period when dams attack unfamiliar intruders that approach the nest in order to defend their pups (Brunton & Russell 2010). Hence, pregnant rats can be reliably exposed to social stress by placing them into a cage with an unfamiliar lactating mother. In our laboratory, pregnant ‘intruder’ rats were exposed to a lactating ‘resident’ (lactation days 2–8) for 10 min/day on five consecutive days from days 16 to 20 of pregnancy (Brunton & Russell 2010).

Pig model of prenatal social stress

Pigs have also been used to model the effects of exposure to social stress during pregnancy. These studies have relevance not only to humans, but also to the welfare of livestock. In European Union (EU) countries, legislation related to the housing conditions for pigs (Council Directive 2001/88/EC, which applies to all pig holdings in EU member states from 1st January 2013) has led to sows being group housed (rather than being individually housed in close-confinement stalls/farrowing crates) to ensure unrestricted movement and social interaction. However, as pigs form a social dominance hierarchy, the consequent mixing of unfamiliar pregnant pigs leads to aggressive behaviour, injury and HPA stress axis activation, providing a model to evaluate adverse offspring outcomes (Jarvis *et al.* 2005).

In the experimental model, a pair of young primiparous pregnant sows are housed in a new pen with two older unfamiliar multiparous (but not pregnant) sows for two 7-day periods in either the second or the third trimester, while control sows remain in their home pen

(with age-matched familiar conspecifics) and are undisturbed during gestation. This social mixing results in the older sows being aggressive towards the younger sows to establish social dominance (Jarvis *et al.* 2005). The socially mixed pregnant young sows display submissive behaviours, decreased weight gain, increased body lesions as a result of aggressive social interactions and increased salivary cortisol levels (Jarvis *et al.* 2005), indicating the activation of the HPA axis (Fig. 1).

Effects of social stress on pregnancy outcomes in rodents

Social stress exposure during pregnancy can negatively affect pregnancy outcomes, though the effects depend upon the frequency and severity of the stress and when during pregnancy the stress occurs. In hamsters, social stress exposure (social defeat by a dominant conspecific) during early pregnancy results in significantly smaller litter sizes and reduced birth weight for both male and female pups (Pratt & Lisk 1991). Moreover, there is a significant reduction in the number of males per litter, indicating selective resorption/spontaneous abortion of males *in utero* (Pratt & Lisk 1991). Similar effects on litter size have also been reported in mice exposed to psychosocial stress (exposure to a rat or rat odour) in early pregnancy (de Catanzaro 1988).

These effects of stress on pregnancy loss are associated with a significant reduction in circulating progesterone levels and can be prevented by exogenous progesterone administration (Pratt & Lisk 1991). Exposure to other types of stressors during early pregnancy has also been shown to reduce circulating progesterone levels in mice (Parker *et al.* 2011), and in women low progesterone levels in early pregnancy can predict miscarriage (Arck *et al.* 2008). In rodents, maintenance of progesterone secretion and hence the pregnancy relies on the action of luteinising hormone (LH) on the corpora lutea. How the effects of social stress on pregnancy loss are mediated is not fully understood; however, the activation of the maternal HPA axis is likely to be involved. Stress elicits a robust HPA axis response in rodents in early pregnancy (Neumann *et al.* 1998, Brunton *et al.* 2008), and reduced progesterone secretion through corticotrophin-releasing hormone (CRH)-mediated suppression of hypothalamic gonadotrophin-releasing hormone (GHRH) secretion and glucocorticoid-mediated inhibition of GHRH secretion from the hypothalamus and LH release from the anterior pituitary is well established (Rivier *et al.* 1986, Kamel & Kubajak 1987, Chrousos *et al.* 1998; Fig. 2).

Reduced litter size and litter weight have been reported in rats exposed to chronic social stress (2 h/day) throughout gestation (Gotz *et al.* 2008). Whereas brief social stress during late pregnancy (10 min/day on days 16–20) in rats does not affect litter size at birth, birth weight is significantly reduced in the

Figure 2 Interactions between the HPA and hypothalamic–pituitary–gonadal (HPG) axes. HPG axis: GNRH neurones in the preoptic area (POA) in the hypothalamus synthesise and secrete GNRH from their terminals at the median eminence (ME). GNRH acts on gonadotrophs in the anterior pituitary gland to stimulate (+) the synthesis and release of LH and follicle-stimulating hormone (FSH) into the blood. In the testis, LH stimulates testosterone production in Leydig cells, while FSH stimulates spermatogenesis. In the ovary, FSH controls follicular maturation and oestradiol (E_2) production, while LH regulates ovulation and progesterone secretion by the corpus luteum. Gonadal sex steroid hormones exert negative feedback (–) actions at the level of the hypothalamus and the anterior pituitary. HPA axis: stress exposure activates CRH neurones in the parvocellular division of the paraventricular nucleus (pPVN) in the hypothalamus, triggering CRH release at the ME. CRH stimulates ACTH release from the anterior pituitary, which in turn stimulates glucocorticoid secretion from the adrenal cortex. Glucocorticoids exert negative feedback control at the level of the anterior pituitary and PVN (see Fig. 1). HPA–HPG axis interactions: glucocorticoids influence the HPG axis at multiple levels. In the hypothalamus, glucocorticoids inhibit the synthesis and release of GNRH, and in the anterior pituitary, glucocorticoids inhibit LH secretion. Glucocorticoid receptors are expressed in the ovaries and testes and glucocorticoids act here to inhibit gonadal steroidogenesis. Increased CRH levels as a consequence of stress also inhibit the GNRH neurones either directly or indirectly via stimulation of β -endorphin in the arcuate nucleus.

prenatally stressed female offspring with a tendency for reduced birth weight in the male offspring (Brunton & Russell 2010). The number of prenatally stressed pups surviving between birth and weaning is also reduced compared with that of controls, and this does not appear to be a result of increased infanticide in gestationally stressed dams (N J Grundwald, Y-T Lai & P J Brunton 2012, unpublished observations). Similarly, overcrowding stress during the second half of pregnancy in mice results in pups of reduced birth weight with no

effect on litter size (Zielinski *et al.* 1991). Maternal HPA axis responses to stress are significantly attenuated in late pregnancy in rats (Brunton *et al.* 2009) and mice (Douglas *et al.* 2003), including in response to social stress (Brunton & Russell 2010), which may explain the contrasting effects of social stress exposure during early and late pregnancy on litter size. While stress during early pregnancy causes robust activation of the maternal HPA axis (Brunton *et al.* 2008), which can mediate the inhibition of progesterone secretion (as described above) and hence pregnancy loss, stress during late pregnancy is not expected to have such an effect on progesterone secretion due to suppressed maternal HPA axis responses (Neumann *et al.* 1998, Brunton *et al.* 2005, 2008), which may protect against pregnancy failure.

Stress-induced pregnancy loss in early gestation may be an adaptive mechanism that minimises investment in a pregnancy in suboptimal conditions and conserves maternal resources/energy for survival, while in late pregnancy, when the mother has already invested significant resources in the foetuses, the pregnancy is maintained despite stress exposure. There are, however, several other detrimental consequences of social stress exposure during pregnancy, especially for the offspring: it seems that where pregnancy loss does not occur *in utero*, foetal programming does. The subsequent sections focus on such adverse effects of prenatal social stress on the offspring in later life.

Effects of prenatal social stress on stress responsivity in the offspring

Stress responsivity in prenatally stressed rodents

Generally, prenatally stressed rodents display greater HPA axis responses to acute stress prior to puberty onset (Henry *et al.* 1994) and in adulthood (Weinstock *et al.* 1992, Henry *et al.* 1994, McCormick *et al.* 1995, Bosch *et al.* 2007, Brunton & Russell 2010) and responses are prolonged compared with those of controls (Henry *et al.* 1994, Barbazanges *et al.* 1996, Brunton & Russell 2010). This is also the case for offspring born to mothers exposed to social stress during pregnancy (Abe *et al.* 2007, Bosch *et al.* 2007, Brunton & Russell 2010), where both the male (Abe *et al.* 2007, Brunton & Russell 2010) and female (Bosch *et al.* 2007, Brunton & Russell 2010) offspring display markedly greater adrenocorticotrophic hormone (ACTH) and corticosterone responses to physical (e.g. immune challenge) and psychological (e.g. restraint and elevated platform exposure) stressors in adulthood compared with control offspring.

Stress responsivity and emotionality in prenatally stressed pigs

Prenatal social stress does not appear to affect piglet birth weight (as has been reported in rodent models of prenatal

social stress (Brunton & Russell 2010)), viability or mortality; however, the female prenatally stressed piglets gain weight more slowly than controls and adapt less well to being separated from their mothers and housed in a novel environment at weaning (Jarvis *et al.* 2005), an event that is considered to be stressful (Mason *et al.* 2003). Moreover, increased serotonin turnover in the hippocampus has been reported in response to weaning in piglets born to socially stressed mothers, which may contribute to increased emotionality (Otten *et al.* 2010).

In response to an acute social stress at 10 weeks, prenatally stressed female pigs (males have not been tested) display increased and more prolonged salivary cortisol responses compared with controls (Jarvis *et al.* 2005), further indicating enhanced stress reactivity in prenatally stressed offspring.

Central mechanisms of enhanced stress reactivity

It is widely considered that the increased susceptibility to adulthood diseases and many of the negative phenotypes observed in prenatally stressed offspring (described above) are underpinned by the dysregulation of the HPA axis (Levitt *et al.* 2000). Therefore, it is appropriate to focus on what is known about the mechanisms involved in altered HPA axis activity in prenatally stressed offspring.

Enhanced ACTH and hence corticosterone responses to stress in the male offspring of rats exposed to social stress prenatally result from increased drive by the ACTH secretagogues, released by parvocellular neurones in the paraventricular nucleus (pPVN) in the hypothalamus, as indicated by greater levels of *Crh* mRNA and arginine vasopressin (*Avp*) mRNA in the pPVN following stress (Brunton & Russell 2010; Fig. 3). Notably, there is a sex difference in the expression profiles of these genes: in contrast to males, only *Crh* mRNA levels and not *Avp* mRNA levels are greater in prenatally stressed females than in controls after an immune challenge (systemic interleukin 1 β ; Brunton & Russell 2010). Nonetheless, greater HPA axis responses to stress in both male and female offspring are evidently the result of increased drive by the hypothalamic CRH neurons in the pPVN (Brunton & Russell 2010).

Consistent with these findings in rodents is the finding of elevated basal *Crh* mRNA expression in the PVN and in the amygdala of female prenatally stressed pigs compared with controls (Jarvis *et al.* 2005). Given the central role of CRH in the regulation of the HPA axis and in angiogenesis (see below; Schulkin *et al.* 1998), this may explain the increased HPA axis reactivity and heightened emotional responses to stressful experiences in the prenatally stressed pigs (Jarvis *et al.* 2005).

The enhanced and prolonged HPA axis responses to stress in the offspring of mothers exposed to social stress during pregnancy are not fully understood; however, impaired negative feedback control has been proposed. The HPA axis is under negative feedback control by

glucocorticoids, which function to terminate stress responses (Fig. 1). In rats, prenatal stress exposure results in the reduced expression of glucocorticoid receptors (GRs; Weinstock *et al.* 1992), mineralocorticoid receptors (MRs; Barbazanges *et al.* 1996) or both GRs and MRs in the hippocampus of the offspring (Henry *et al.* 1994), depending on the nature and timing of the prenatal stress exposure and the sex of the offspring. In the case of prenatal social stress, *Nr3c2* (*Mr*) mRNA expression is significantly reduced in the hippocampus of the male and female offspring (Brunton & Russell 2010), whereas *Nr3c1* (*Gr*) mRNA expression is largely unaffected in either the hippocampus or the PVN (Brunton & Russell 2010) (Fig. 3). Thus, reduced hippocampal MR expression may contribute to impaired feedback control of the HPA axis, but this is yet to be functionally tested.

The mechanism by which hippocampal corticosteroid receptor expression is reduced in prenatally stressed offspring is unclear. Nevertheless, GRs and MRs can be detected in the foetal hippocampus from gestational days 13 and 16 respectively (Diaz *et al.* 1998); thus, it is conceivable that the elevated levels of maternal glucocorticoids could interact with the *Nr3c1* and/or *Nr3c2* promoters to alter gene expression. Epigenetic mechanisms could provide a means through which gene expression is permanently altered in prenatally stressed animals. For example, in mice, the adult male offspring of mothers exposed to chronic variable stress during early pregnancy exhibit hyperactive HPA axis responses to stress, concomitant with increased *Crh* mRNA expression in the PVN and reduced hippocampal *Nr3c1* mRNA expression (Mueller & Bale 2008). This is associated with hypomethylation of the *Crh* promoter and hypermethylation of the *Nr3c1* gene (Mueller & Bale 2008), consistent with the up- and down-regulation of *Crh* and *Nr3c1* gene expression respectively.

Effects on anxiety-like behaviour in prenatally stressed offspring

Adult male offspring of rats exposed to social stress during pregnancy display increased anxiety-related behaviour on the elevated plus maze (Brunton & Russell 2010) and in the open field (Abe *et al.* 2007) and increased depression-like behaviour in a forced swim test (Abe *et al.* 2007), consistent with the findings of studies using other prenatal stress paradigms (Poltyrev *et al.* 1996, Vallee *et al.* 1997). By contrast, prenatal social stress in late pregnancy does not appear to affect anxiety-type behaviour in female offspring (Brunton & Russell 2010), except when given in combination with another psychological stressor (restraint) in early-mid pregnancy (Bosch *et al.* 2007). Other studies using different prenatal stress models in rats have also reported sex differences (Zagron & Weinstock 2006, Mueller & Bale 2008), including reduced anxiety in

Figure 3 Changes in the brain of the offspring following prenatal social stress. Summary diagram illustrating the major differences in mRNA expression found in the brain of adult male prenatally stressed rats (mother was exposed to social stress, 10 min/day on days 16–20 of pregnancy) compared with control male offspring, under basal conditions (left) and following stress (right; 4-h post-interleukin 1β administration). ↑, Greater expression; ↓, lower expression and ↔, no difference in mRNA expression compared with that in control rats. 3V, third ventricle; BLA, basolateral amygdala; BMA, basomedial amygdala; CeA, central amygdala; CRH-R1, CRH receptor type 1; MeA, medial amygdala; OT, optic tract. Data are based on the studies of Brunton & Russell (2010) and Brunton *et al.* (2011).

prenatally stressed females compared with males (Zuena *et al.* 2008).

CRH neurones in the central nucleus of the amygdala (CeA) are considered to be particularly important in the mediation of anxious behavioural responses (Schulkin *et al.* 1998); hence, central administration of CRH induces anxiety-like behaviour (Dunn & Berridge 1990), while a CRH antagonist given centrally can block fear responses in prenatally stressed rats (Ward *et al.* 2000). Therefore, increased anxiety-like behaviour in prenatally stressed rats may be mediated via enhanced central CRH release or action (Dunn & Berridge 1990).

Both male and female offspring of dams exposed to social stress during pregnancy have increased levels of *Crh* mRNA in the CeA (Brunton & Russell 2010; Fig. 3), consistent with the finding of increased CRH content and mRNA expression in the amygdala from other prenatal stress models in rats (Cratty *et al.* 1995) and mice (Mueller & Bale 2008) and in the offspring of pigs whose mothers were exposed to social stress during gestation (Jarvis *et al.* 2005). These changes probably involve facilitation by glucocorticoids, as glucocorticoids up-regulate *Crh* gene expression in the amygdala (Makino *et al.* 1994) and central GRs facilitate anxiety-type behaviours; moreover, *Nr3c1* mRNA levels are

up-regulated in the amygdala in prenatally stressed rats (McCormick *et al.* 1995, Brunton & Russell 2010). However, this does not explain the increased anxiety-related behaviour in the male offspring of mothers exposed to social stress during pregnancy as both sexes exhibit elevated *Crh* mRNA expression in the CeA, but only the males exhibit an anxious phenotype (Brunton & Russell 2010). Nonetheless, altered CRH receptor expression may play a role in this sex difference.

There are two CRH receptors through which CRH exerts its actions. The activation of the type 1 receptor (CRH-R1) mediates HPA axis responses and anxiety-like behaviours, whereas that of the type 2 receptor (CRH-R2) mediates the anxiolytic actions of urocortins 2 and 3 (Bale & Vale 2004). The expression of mRNA for the two CRH receptors is altered by prenatal social stress, and importantly there are distinct sex differences (Brunton *et al.* 2011). In prenatally stressed males, but not in females, *Crhr1* mRNA levels are greater in the CeA and basolateral amygdala than in those in unstressed controls (Brunton *et al.* 2011; Fig. 3). Moreover, *Crhr2* mRNA expression is reduced in the basomedial amygdala (BMA) in prenatally stressed males (Fig. 3) and increased in the BMA in prenatally stressed females (Brunton *et al.* 2011). This differential CRH receptor mRNA expression

in the amygdaloid complex in prenatally stressed males and females may underlie the difference in anxiety-like behaviour following social stress exposure in late gestation. Indeed, in other prenatal stress models where both sexes exhibit heightened anxiety, reduced *Crhr2* expression is observed in the amygdala in both sexes (Zohar & Weinstock 2011). It is not known whether these changes in CRH receptor expression in the amygdala result from changes in DNA methylation in the promoter regions of the CRH receptor genes, as has been shown for *Crhr1* mRNA expression in the PVN in anxious male offspring of mothers exposed to hypoxia throughout gestation (Wang *et al.* 2013).

Effects on nociception in prenatally stressed offspring

There is also evidence from pigs that maternal exposure to social stress during gestation induces alterations in sensitivity and responsiveness to pain in the offspring. Tail-docking is a routine husbandry practice (to prevent injury by tail-biting), which is performed in the early postnatal period (~3 days old) without anaesthesia/analgesia (Hunter *et al.* 2001). Piglets born to mothers exposed to social stress during pregnancy exhibit significantly greater pain scores (independent of sex) in response to tail-docking compared with tail-docked piglets born to control sows (Rutherford *et al.* 2009), indicating that prenatally stressed piglets are more sensitive to pain. Remarkably, the pain score in the piglets positively correlates with maternal cortisol levels during the social stress (Rutherford *et al.* 2009), indicating that nociception in the offspring is influenced by the gravity of the mother's stressful experience. Similar findings have been observed in humans: the greater the levels of maternal cortisol and maternal psychosocial stress experienced in a woman during pregnancy, the greater her newborn baby's behavioural and cortisol response to a painful event after birth (heel prick blood test; Davis *et al.* 2011).

In contrast to findings in neonatal prenatally stressed piglets, studies assessing nociception after weaning (age 5–8 weeks) have found that prenatal stress is associated with increased nociceptive thresholds (e.g. hypoalgesia) in response to noxious mechanical or cold stimulation under basal conditions and in response to acute inflammation in both sexes, indicative of reduced sensitivity to pain (Sandercock *et al.* 2011). Hence, while prenatally stressed pigs are more behaviourally reactive to a painful challenge (tail-docking) in the neonatal period, it appears that basal nociception and inflammation-evoked nociception are reduced in later life in prenatally stressed pigs. This indicates a possible divergence in responses to the sensory and affective components of pain in prenatally stressed pigs. Whether this is a result of changes in stress-induced analgesia requires further investigation. However, it is interesting to note that stress-induced analgesia interacts

with behavioural performance in an inverted U-shape, with mild stress facilitating and more severe stress disrupting appropriate behavioural responses (Amit & Galina 1988).

Effects on metabolism

It has recently been shown that prenatal social stress also has sex-dependent effects on glucose, insulin and lipid homeostasis in the adult offspring (Brunton *et al.* 2013). Prenatal stress is associated with stress-induced hyperglycaemia in males, but not in females, and with hyperinsulinaemia in response to glucose loading in females, but not in males (Brunton *et al.* 2013). Moreover, the expression of genes important in glucocorticoid and lipid metabolism is altered by prenatal social stress predominantly in the liver and skeletal muscle in the male rats, whereas in female rats the majority of changes are observed in subcutaneous fat (Brunton *et al.* 2013). Thus, prenatal social stress exposure is associated with sex-specific alterations in the periphery that indicate increased insulin resistance and an increased risk of metabolic dysfunction in adulthood.

Effects on the reproductive axis and reproductive behaviours in the offspring

Limited evidence from studies in pigs indicates that prenatal exposure of pregnant sows to social stress may also affect the development of the reproductive axis in the male and female offspring (Ashworth *et al.* 2011). In pre-pubertal females, prenatal stress significantly reduces the number of primordial follicles in the ovaries (Ashworth *et al.* 2011). The long-term effects of this are unclear; however, studies in women indicate that the ovarian follicle pool may predict reproductive capacity in later life. Hence, the number of primordial follicles prior to puberty onset governs the rate at which primordial follicles are recruited for folliculogenesis: the number of follicles recruited is inversely proportional to the number of primordial follicles (Gougeon *et al.* 1994). Thus, assuming that primordial follicles are depleted more rapidly, one may predict premature reproductive senescence in prenatally stressed females, though this requires further study.

In pre-pubertal male pigs, prenatal stress is associated with a significant reduction in the circulating levels of the sex steroids, testosterone and oestradiol. Whether this altered steroidogenesis in prenatally stressed males will be a factor in future reproductive capacity is not known, but it warrants further investigation. Reduced testosterone levels are of particular interest, since in rats prenatal stress exposure blocks the normal prenatal surge in circulating testosterone levels that occurs in male fetuses in late gestation (Ward & Weisz 1980), and

this block results in the demasculinisation and feminisation of sexual behaviours in adulthood (Ward 1972). Moreover, given that testosterone is known to exert inhibitory actions over HPA axis activity and anxiety behaviour (Handa *et al.* 1994, Edinger & Frye 2005), reduced testosterone levels in prenatally stressed male pigs may predict a propensity for increased stress reactivity (as has been described above for female prenatally stressed pigs). Indeed, reduced testosterone levels have been shown to underpin increased stress reactivity and increased behavioural indicators of anxiety in a guinea pig model of prenatal stress (Kapoor & Matthews 2011).

To date, few studies have directly assessed the effects of social stress exposure during pregnancy on the future reproductive capacity of the offspring in rodents. In rats exposed to chronic social stress (2-h daily exposure to a dominant female) throughout pregnancy, no effects on reproductive parameters were found in the F1 female offspring, such as age at which their first litter was produced and the total number of litters and number of pups produced; however, the time of day at which prenatally stressed females gave birth was shifted from the light phase to the dark phase (Gotz *et al.* 2008). Nevertheless, other prenatal stress models (exposure to repeated restraint under bright lighting for 7 days in late pregnancy) have reported altered reproductive behaviours in prenatally stressed F1 females at the time of mating, including increased aggression towards the male, increased avoidance of the male, reduced solicitation behaviour, and reduced incidence and intensity of lordosis (Frye & Orecki 2002), and impaired adult male sexual performance (Holson *et al.* 1995). Moreover, the male rats of mothers exposed to immobilisation (2 h/day for 5 consecutive days) in late gestation show reduced sexual motivation towards and reduced copulatory activity with receptive females in adulthood (Wang *et al.* 2006). It is not yet known whether similar effects can be observed in rodents following prenatal social stress exposure; however, the social stress of overcrowding during pregnancy is associated with masculinisation of female pups (Zielinski *et al.* 1991).

Effects on maternal behaviour in the female offspring

Maternal behaviour in rodents

While we did not find any differences in the subsequent maternal behaviour of rats exposed to social defeat during late pregnancy (N J Grundwald & P J Brunton 2012, unpublished observations), one study has reported reduced mother–pup interactions following social crowding during the last week of pregnancy (Moore & Power 1986). This was reflected by reduced anogenital licking of the pups by the dam and intriguingly occurred regardless of the pups being reared by their biological

mother (hence gestationally stressed) or by an unstressed foster mother, indicating that the prenatally stressed pups elicit less maternal licking (Moore & Power 1986). These data are of particular interest with regard to the future sexual behaviour of the offspring, considering that male pups generally receive more anogenital licking than females, an effect that is mediated by testosterone-dependent cues (Moore 1982), and because both prenatal stress and decreased maternal licking of pups are associated with deficits in male sexual behaviour in later life (Ward 1972, Moore 1984).

Prenatal social stress has also been shown to negatively affect maternal care in the female F1 offspring when they themselves become mothers (Bosch *et al.* 2007). Prenatally stressed dams exhibit lower levels of nursing behaviour and spend less time in direct contact with their pups compared with controls (Bosch *et al.* 2007). This is associated with elevated levels of *Crh* mRNA in the pPVN under basal conditions. It is not known whether prenatal social stress affects CRH expression in other regions of the brain; however, as the activation of the central CRH system is known to impair maternal behaviour (Pedersen *et al.* 1991, Gammie *et al.* 2004, Klampfl *et al.* 2013), this may contribute to reduced mother–pup interactions and reduced nursing.

Maternal behaviour in pigs

While socially mixed mothers do not show any differences in maternal behaviour *post partum* compared with control sows, interestingly and as in rats, when their female offspring become mothers, deficits in maternal behaviour can be observed, including a tendency to be more aggressive towards their piglets (Jarvis *et al.* 2005). This altered maternal behaviour is associated with an anxiety-prone phenotype and altered CRH receptor expression in the amygdala in the prenatally stressed females (K Rutherford 2012, personal communication).

Thus, prenatal stress exposure evidently exerts a long-term effect on future behaviour. Given that postnatal maternal care has also been shown to programme stress responsivity and emotionality in the offspring (Champagne & Meaney 2001, Weaver *et al.* 2004) and furthermore to programme subsequent maternal behaviour in female offspring (Champagne & Meaney 2001, Palombo *et al.* 2010), a further consequence of prenatal social stress is the potential transmission of the programmed phenotype to future generations.

Transmission of prenatal stress effects from the mother to the foetus

The mechanisms responsible for the transmission of the effects of maternal stress to the foetus(es) are unclear; however, maternal glucocorticoids and/or

catecholamines, foetal HPA axis responses and deficits in maternal behaviour may all play a role and are discussed below.

Role for glucocorticoids?

The exposure of the foetus(es) to excessive levels of maternal glucocorticoids as a result of stress has been proposed (Barbazanges *et al.* 1996, Welberg & Seckl 2001) as one mechanism whereby the effects of maternal stress may be transmitted to the offspring. Pregnant rats or guinea pigs treated with a synthetic glucocorticoid (dexamethasone) produce offspring with phenotypes similar to those exposed to prenatal stress (Welberg *et al.* 2001, Kapoor & Matthews 2005). Furthermore, maternal adrenalectomy (to prevent stress-induced increases in the levels of maternal glucocorticoids) abrogates some of the effects of prenatal stress in the offspring (Barbazanges *et al.* 1996). Nevertheless, a role for maternal glucocorticoids is debatable for two reasons. First, the placenta expresses 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2; Benediktsson *et al.* 1997), which acts as a barrier to limit the exposure of the foetus to active maternal glucocorticoids by metabolising corticosterone/cortisol (depending on the species) into inactive 11-dehydrocorticosterone/cortisone. Dexamethasone is a synthetic glucocorticoid and is not a substrate for 11 β -HSD2; therefore, it can freely cross the placenta. Second, and as has been mentioned above, maternal HPA axis responses to stress are markedly attenuated in late pregnancy (Brunton *et al.* 2008).

Although repeated social stress in late pregnancy evokes maternal corticosterone secretion, the amplitude and duration of the response are drastically reduced in comparison with those in virgin rats (Brunton & Russell 2010); moreover, the maximal levels of corticosterone achieved do not exceed those levels observed at the diurnal peak in gestation (Atkinson & Waddell 1995). Despite this, the offspring of these socially stressed dams exhibit programmed phenotypes (e.g. reduced birth weight, increased HPA axis responses to stress and increased anxiety-like behaviour; Brunton & Russell 2010), as has been described above, casting doubt on whether maternal glucocorticoids mediate the effects of maternal stress on the offspring. Nevertheless, the timing of elevated circulating corticosterone levels may be critical: an unanticipated peak in corticosterone secretion during the circadian nadir may in some way contribute to programming the foetuses *in utero*. Furthermore, exposure to repeated stress in late pregnancy significantly reduces the capacity to up-regulate the activity of placental 11 β -HSD2 (Welberg *et al.* 2005), which means potentially increased exposure of the foetuses to maternal glucocorticoids. Lastly, in rats, the foetal adrenal glands are sufficiently developed to begin secreting glucocorticoids from

embryonic day 16, and the foetal HPA axis is activated in response to maternal stress in late pregnancy (Ohkawa *et al.* 1991, Fujioka *et al.* 2003), giving rise to the possibility that glucocorticoids of foetal origin may contribute to programming of the foetal brain.

Role for catecholamines?

The removal of the maternal adrenal glands (as has been described above) not only removes the source of glucocorticoids but also removes other adrenal factors (e.g. catecholamines, sex steroids and their precursors, mineralocorticoids and opioids), some of which may also play a role in foetal programming. In late pregnancy, stress-induced adrenaline release from the adrenal medulla is reduced compared with that in non-pregnant rats (Vaha-Eskeli *et al.* 1992, Russell *et al.* 2008); however, noradrenaline responses are maintained, reflecting sympathetic nervous system activation (Vaha-Eskeli *et al.* 1992, Russell *et al.* 2008). Placental monoamine oxidase and catechol-*O*-methyltransferase metabolise maternal noradrenaline (Chen *et al.* 1974, 1976), but up to 12% can be transferred to the foetal compartment (Sodha *et al.* 1984), which may have adverse effects on the foetus(es). Elevated levels of circulating maternal catecholamines cause vasoconstriction of placental blood vessels, reducing placental blood supply and hence impairing the delivery of oxygen and nutrients to the foetuses. Given that hypoxia and nutrient restriction activate the foetal HPA axis (Edwards & McMillen 2002, Roelfsema *et al.* 2005) and elicit foetal sympathetic-adrenomedullary stress responses (Gu & Jones 1986), these responses may contribute to the foetal programming of HPA axis responsivity and anxiety-like behaviour in the adult offspring (Almeida *et al.* 1996, Lingas & Matthews 2001, Nunez *et al.* 2008, Fan *et al.* 2009, Wang *et al.* 2013). The adrenal medulla also secretes β -endorphin following stress exposure, which may cross the placenta to influence the development of the foetal brain (Sandman *et al.* 1997).

Altered maternal behaviour?

Given that some of the models of prenatal stress alter *post partum* maternal behaviour (Moore & Power 1986, Smith *et al.* 2004), it is important to take this into consideration in attempting to explain how the effects of stress during pregnancy are transmitted to the offspring. The early postnatal environment plays an important role in influencing HPA axis activity and anxiety-like behaviour in later life (Liu *et al.* 1997, Champagne & Meaney 2001). A high level of maternal care is associated with reduced HPA axis responses to stress and reduced anxiety-like behaviour in the adult offspring, whereas low levels of maternal care or long periods of maternal separation produce the opposite

effects in the offspring (Liu *et al.* 1997, Champagne & Meaney 2001). The mechanisms responsible involve epigenetic programming of the glucocorticoid feedback regulation of the HPA axis (Weaver *et al.* 2004). Thus, prenatal stress paradigms that result in deficits in maternal behaviour *post partum* may also contribute to the programming of the offspring.

Reversal of foetal programming effects induced by stress exposure in pregnancy

Role for neurosteroids?

Studies attempting to reverse the programming effects of prenatal stress exposure are ongoing. The neurosteroid metabolites of the sex steroids, progesterone and testosterone, are a particular focus for several reasons. First, as has been mentioned above, several prenatal stress paradigms have demonstrated consequent masculinisation of the female offspring and/or demasculinisation/feminisation of the male offspring (Ward 1972, Zielinski *et al.* 1991, Holson *et al.* 1995, Wang *et al.* 2006), indicating that prenatal stress interferes with the development of the hypothalamic–pituitary–gonadal axis (Fig. 2). Second, the normal post-pubertal sex differences in HPA axis function, whereby responses to stress in females exceed those observed in males, can be explained by differences in the types of sex steroids produced: specifically, testosterone reduces while oestrogen enhances HPA axis responses to stress (Handa *et al.* 1994). Finally, the 5α -reduced metabolites of progesterone and testosterone, allopregnanolone and androstandiol, respectively have been shown to have anxiolytic actions and to suppress HPA axis responses to stress (Patchev *et al.* 1994, 1996, Frye & Rhodes 2006, Lund *et al.* 2006, Brunton *et al.* 2009), implicating them as putative candidates for normalising the stress-hyperactive and -anxious phenotype in prenatally stressed animals.

Prenatal stress exposure has been linked to reduced levels of allopregnanolone, due to reduced conversion of progesterone to its 5α -reduced metabolites (5α -dihydroprogesterone and allopregnanolone), in the brains of juvenile rats and similarly to reduced levels of the 5α -reduced metabolite of testosterone dihydrotestosterone in the brain of adult male offspring (Paris & Frye 2011, Paris *et al.* 2011, Walf & Frye 2012). These data indicate reduced neurosteroidogenesis in prenatally stressed offspring, probably as a result of reduced 5α -reductase activity. Indeed, there is evidence for reduced central (P J Brunton & J A Russell 2012, unpublished observations) and hepatic (Brunton *et al.* 2013) expression of 5α -reductase mRNA in offspring exposed to prenatal social stress, which may contribute to reduced neurosteroid levels in the brain.

Short-term allopregnanolone treatment has been shown to normalise HPA axis responses to an acute

stress challenge in adult female but not in male prenatally stressed rats. However, in prenatally stressed males, the 5α -reduced metabolite of testosterone, androstandiol, is effective (P J Brunton, M V Donadio & J A Russell 2012, unpublished observations). Similarly, postnatal testosterone administration ameliorates behavioural deficits and elevates HPA axis function in prenatally stressed guinea pigs (Kapoor & Matthews 2011). Whether this is a direct effect of testosterone actions or is mediated via testosterone metabolites (e.g. dihydrotestosterone and/or androstandiol) has not been tested. Nevertheless, 5α -reduced steroids can evidently overwrite foetal programming by prenatal social stress, at least in terms of exaggerated HPA axis responses. In support of this is the finding that if allopregnanolone is administered to pregnant dams at the same time as they are exposed to gestational stress, enhanced anxiety behaviour in the juvenile and adult offspring is prevented (Zimmerberg & Blaskey 1998). Whether postnatal allopregnanolone or androstandiol treatment exerts similar effects on anxiety-like behaviour or indeed reverses the impact of prenatal social stress on the other negative phenotypes observed in the offspring is as yet unknown.

Postnatal environmental manipulations

Brief maternal separation with neonatal handling produces persistent changes in HPA axis responsivity (Levine 1967). As adults, neonatally handled rats exhibit markedly attenuated HPA axis responses to stress concomitant with enhanced glucocorticoid negative feedback control of the HPA axis (Meaney *et al.* 1989). The effects of neonatal handling appear to be mediated by increased maternal care when the pups are returned after the brief separation (Liu *et al.* 1997). The manipulation of maternal care by brief neonatal handling has been shown to reverse the behavioural abnormalities (e.g. increased anxiety) associated with prenatal stress and to normalise HPA axis responses to stress (Wakshlak & Weinstock 1990, Smythe *et al.* 1996, Vallee *et al.* 1997), although it is not known whether similar postnatal manipulations reverse foetal programming effects induced by prenatal social stress. The central mechanisms that underlie handling-induced changes in behavioural and neuroendocrine responses to stress are not fully understood; however, changes in GABAergic inhibition in the brain may be involved (Hsu *et al.* 2003), which is noteworthy given the potent effects that neurosteroids exert via GABA_A receptors (Belelli & Lambert 2005).

Summary and conclusions

In this article, the evidence that social stress exposure during pregnancy has detrimental effects on the

pregnancy and the offspring has been reviewed. Pregnancy outcomes depend upon when during gestation the stress is experienced, with stress in early gestation typically resulting in pregnancy loss, whereas later in gestation the pregnancy is maintained, although birth weights of the newborn(s) are significantly reduced and the prenatal stress has long-lasting programming effects on various systems in the offspring. In later life, prenatal social stress is generally associated with offspring that are hyper-responsive to stress and more anxious, as a result of changes in their brain. There are also indicators that the capacity to reproduce and reproductive/social behaviours may also be negatively affected. The finding that prenatal stress can programme future maternal behaviour highlights the potential for negative phenotypes to be transmitted to future generations.

Together, these findings have implications both for animal welfare in relation to livestock husbandry practices and for the management of pregnancy in women. Many epidemiological studies support the hypothesis that the experience of either physical or psychological stress in women during pregnancy can adversely programme their offspring. For example, there is an increase in the propensity for mild cognitive impairments and behavioural problems in children following prenatal stress (Laplante *et al.* 2008, Buss *et al.* 2012, Sandman *et al.* 2012) and increased susceptibility to develop cardiovascular and metabolic disease and neuropsychiatric disorders in later life (Entringer *et al.* 2008, Bale *et al.* 2010, Reynolds 2013).

Understanding how the effects of maternal stress during pregnancy are transmitted to the foetus(es) and the mechanisms involved in foetal programming as a result could aid the development of postnatal therapeutic interventions to reverse the detrimental effects observed in the offspring. In particular, understanding how resetting the activity of the HPA axis in offspring occurs following prenatal stress has important implications for humans since HPA axis hyperactivity is considered to underpin several adulthood pathologies (Phillips *et al.* 1998, Levitt *et al.* 2000). The prospects that adverse programming effects may be reversed by postnatal environmental manipulations or with neurosteroid administration are exciting areas that warrant further research.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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