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Giving a good start to a new life via maternal brain allostatic adaptations in pregnancy

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ABSTRACT

Successful pregnancy requires adjustments to multiple maternal homeostatic mechanisms, governed by the maternal brain to support and enable survival of the growing fetus and placenta. Such adjustments fit the concept of allostasis (stability through change) and have a cost: allostatic load. Allostasis is driven by ovarian, anterior pituitary, placental and feto-placental hormones acting on the maternal brain to promote adaptations that support the pregnancy and protect the fetus. Many women carry an existing allostatic load into pregnancy, from socio-economic circumstances, poor mental health and in 'developed' countries, also from obesity. These pregnancies have poorer outcomes indicating negative interactions (failing allostasis) between pre-pregnancy and pregnancy allostatic loads. Use of animal models, such as adult prenatally stressed female offspring with abnormal neuroendocrine, metabolic and behavioural phenotypes, to probe gene expression changes, and epigenetic mechanisms in the maternal brain in adverse pregnancies are discussed, with the prospect of ameliorating poor pregnancy outcomes.

1. Introduction

A successful pregnancy outcome requires adaptations to several homeostatic systems in the mother. Such adjustments fit the concept of allostasis (stability through change), however, these changes have a cost: allostatic load. Here we consider first the concepts of allostasis and allostatic load, in relation to human pregnancy, and then review related studies using animal (primarily rat) models. The latter are aimed at revealing allostatic mechanisms in specific systems, and the adverse programming of offspring that may arise despite these mechanisms, which can even be transferred to subsequent generations.

2. Allostasis

The concept of "allostasis" or "stability through change" was proposed by Sterling and Eyer in 1988 (Sterling and Eyer, 1988) as a major modification of the traditional concept of a constant internal milieu, proposed by Claude Bernard (Bernard, 1865, 1974) and extended by Walter B Cannon (Cannon, 1929, 1932), to include regulation through 'homeostasis', involving physiological mechanisms with presumed 'set-points' for each system.

Sterling argued that the 'concept of homeostasis is flawed: the goal of regulation is not to preserve constancy of the internal milieu, but to continually adjust the milieu to promote survival and reproduction' (Sterling, 2012). Sterling asserted that feedback is inefficient for this, and ''allostasis' proposes that efficient regulation requires anticipating needs and preparing to satisfy them before they arise', with minimal energy cost. Moreover, he recognised that the strategy necessarily requires the brain (Sterling, 2012); here we add, it involves specifically neuroendocrine mechanisms.

2.1. Pregnancy allostasis

Sterling's description perfectly describes the situation in pregnancy, which can thus be defined as an allostasis condition, as recognised by Power and Schulkin (Power and Schulkin, 2012), organised and regulated by the maternal brain, which receives and interprets endocrine signals from, among other sources, the conceptus (Russell and Brunton, 2014). Considering pregnancy, Power and Schulkin (2012) proposed a modified definition of allostasis as "achieving viability [instead of 'stability'] through change", and for homeostasis 'achieving viability [instead of 'stability'] through resistance to change' (Power and Schulkin, 2012). For example, the suppression of cyclical activity of the maternal hypothalamo-pituitary-gonadal (HPG) axis by the ovarian and placental hormones of pregnancy is an allostatic change, averting the possibility of a further pregnancy for the duration of the present

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gestation. Suppressed HPG activity means a huge investment in the ongoing pregnancy- with moderation of risk for a woman by pre-pregnancy and ante-natal choices and expert care. For other species, a favorable outcome is governed by multiple births and frequent pregnancy, or natural post-natal wastage as in polytocous predated species (Kroeger et al., 2018).

2.2. Allostatic load

McEwen (McEwen and Stellar, 1993; McEwen, 1998) recognised that the individual's responses to chronic or repeated stress involves allostasis, affecting neuroendocrine, immune and autonomic systems and the brain, with chronic activation of regulatory systems. McEwen (McEwen, 1998) also proposed that activation of allostatic mechanisms can be expected to strain the systems involved, in the context of chronic or repeated stress. He called the consequent 'wear and tear' 'allostatic load', which we consider, in the context of pregnancy, also includes the cost of allostasis in terms of additional energy expenditure (Ladyman et al., 2018).

Hence, the multi-system adaptations that are essential for successful pregnancy can also be considered to result in allostatic load, or in pregnancy 'metabolic or regulatory load' may be a more appropriate description (Power and Schulkin, 2012). Obvious examples are increased appetite, energy storage, major cardiovascular and body fluid changes, and exposure to high concentrations of several hormones (Brunton and Russell, 2008; Russell and Brunton, 2014). Nonetheless, endurance of the allostatic load of pregnancy would seem to be, by definition, a remarkable example of resilience in the face of change (Karatsoreos and McEwen, 2013; McEwen, 2016).

2.2.1. Stress and allostatic load

McEwen and others devised measures of allostatic load as a consequence of chronic or high levels of stress, based on readily measured biomarkers reflecting neuroendocrine, immune, cardiovascular and metabolic function, which have validated the clinical usefulness of an allostatic load index in predicting morbidity and mortality (McEwen and Seeman, 1999; Gruenewald et al., 2006; Buckwalter et al., 2016). Factors included in an allostatic load index vary according to the underlying disturbance. For chronic social stress, these include: levels of stress hormones (cortisol, catecholamines, adrenaline, noradrenaline, DHEA-S (dehydroepiandrosterone-sulphate/androstenolone)), cytokines (e.g. interleukin-6), blood pressure, waist/hip ratio, serum high density lipoprotein (HDL), total cholesterol, glycosylated haemoglobin (Gruenewald et al., 2006). The values may be organised using recursive partitioning into cause and effect, grouped into quartiles and summed, or a number of raised values counted to generate an allostatic load index, which predicts, for example, cardiovascular disease over several years (Gruenewald et al., 2006). More complex analyses (using 20 biomarkers) have been made to test links to specific diseases (23 health outcomes) (Buckwalter et al., 2016). A reduced allostatic load index has been developed and validated for use in the work-place (Mauss et al., 2015).

The view has been expressed that 'allostasis be considered a dysregulatory (or disordered) form of physiological regulation' (Ramsay and Woods, 2014). This re-definition seeks to restrict use of 'allostasis' to disease states, and while this can be useful, we regard exclusion of adaptive physiological states, such as normal pregnancy, as inappropriate, and here we use 'allostasis' as originally proposed (Sterling and Eyer, 1988; Sterling, 2012), and reiterated by others, e.g. 'Regulation around an altered apparent steady-state is the essence of allostasis' (Goldstein and Kopin, 2007). The type of allostasis related to illness and energy deprivation has been categorized as Type 1 allostasis, and Type 2 allostasis describes adaptation ('predictive plasticity') to, for example, psychosocial stress, metabolic syndrome and pregnancy (McEwen and Wingfield, 2003; Chatzitomaris et al., 2017). Here, in the context of pregnancy we will use simply 'allostasis'.

2.2.2. Allostatic load in human pregnancy

The standard markers of allostatic load from chronic stress listed in Section 2.2.1 (reflecting cardiovascular, metabolic and inflammatory functions; as in National Health and Nutrition Examination Survey (NHANES) reproductive-health questionnaire), with some modifications, have been used in studies of outcomes of human pregnancy. Allostatic load indices have been assessed for women entering, or completing pregnancy, with or without pre-existing allostatic load from stress or obesity or socio-economic status or trans-generational epigenetic factors (Patchen et al., 2016). However, and perhaps unsurprisingly, allostatic load biomarkers differ between pregnant and non-pregnant women, so interpretation of pregnancy values has been questioned (Morrison et al., 2013). The biomarkers have been selected as indicators of chronic stress without pregnancy, and physiological allostatic changes within normal pregnancy likely necessitate different interpretations e.g. in human pregnancy a tendency to diabetes mellitus is common (Power and Schulkin, 2012) (see Section 3, below), while the human placenta produces corticotropin-releasing hormone (CRH) and metabolises glucocorticoid, which complicate maternal hypothalamo-pituitary-adrenal (HPA) axis assessment (Alcantara-Alonso et al., 2017). Nonetheless differences among pregnant women can be meaningful.

2.2.2.1. Preterm birth. Multiple maternal variables (ethnic, cultural, socio-economic, age, parity) that may affect allostatic load are taken into account in well-designed studies, which have assessed the impact of allostatic load measured at prenatal, mid-pregnancy and post-partum stages on pregnancy outcome. For instance, allostatic load before conception is greater in black American women than in white women, which may be related to living in an impoverished area, as higher allostatic load is associated with adverse socio-economic circumstances (Wallace et al., 2013). In this study, on a large number of women (n = 866, who met strict study criteria from an initial cohort of 1.3 million women), allostatic load was assessed from nine biomarkers: systolic (SBP) and diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, glucose, insulin, and waist circumference: allostatic load scores were generated by summing the number of biomarkers indicating highest risk, i.e. in the top 25th percentile; hence 9 is a high score, 0 is a low score for allostatic load (Wallace et al., 2013). However, prenatal allostatic load was not associated with preterm birth (< 37 weeks) or low birth weight (< 2.5 kg) (Wallace et al., 2013). By contrast, greater allostatic load at the end of the second trimester (assessed as cholesterol, glycosylated hemoglobin (HbA1c), dehydroepiandrosterone-sulphate (DHEA-S), cortisol, and SBP) is inversely correlated with gestational age at birth (Wallace and Harville, 2013). As a consequence, examining allostatic load has been a particular focus in better understanding the causes of preterm birth (Olson et al., 2015). Adverse experiences of the mother in childhood, especially if continuing into adulthood, and depression in pregnancy are strongly related to preterm birth (Olson et al., 2015).

2.2.2.2. Maternal well-being in pregnancy. Allostatic load assessed in early pregnancy correlates positively with poor sleep in pregnancy and lower education level, and notably with incidence of pre-eclampsia (Hux and Roberts, 2015; Hux et al., 2017). In the former prospective study on pre-eclampsia, a pregnancy-specific allostatic load index based on 9 factors across 3 domains was used to assess allostatic load in early pregnancy (< 15 weeks): the factors were: DBP, SBP, pulse pressure (cardiovascular domain); pre-pregnancy body mass index (BMI), cholesterol, HDL, triglycerides (metabolic domain); c-reactive protein, interleukin-6 (inflammatory domain); the outcome showed that higher allostatic load in early pregnancy increased odds of pre-eclampsia, and did so more strongly than obesity (Hux and Roberts, 2015).

Allostatic load assessed post-partum is associated with adverse perinatal outcome including pre-eclampsia, gestational diabetes

mellitus, preterm birth and low birth weight (Hux et al., 2014; Accortt et al., 2017), and the problem of perinatal maternal distress has been identified as appropriate for analysis of allostatic load (Premji, 2014). Allostatic load has been included in an investigative model for large community studies of causal pathways determining the outcomes of pregnancy from a public health perspective (Ramey et al., 2015). Obesity is a major prevalent source of allostatic load in pregnancy, as reviewed next.

3. Obesity and pregnancy

3.1. Obesity

Increasing prevalence of obesity in young women, especially in the more prosperous regions of the world poses increasing risk of pregnancy complications. A recent retrospective study of 18,000 pregnancies in the USA across 9 years showed continuing greater than recommended weight gain in more than 50% of pregnancies (Power et al., 2018). A study of risks associated with obesity in pregnancy, used body mass index (BMI: weight (kg)/height squared (metres^2) at 10–14 weeks gestation as a proxy measure of obesity at the start of pregnancy (Weiss et al., 2004). The study found increasing risk for gestational diabetes mellitus with greater BMI. In a sample of 6102 pregnancies the odds ratio for gestational diabetes mellitus was 1 for lean (BMI $<$ 30; 61%), 2.6 for obese (BMI 30–34.9, 24%), and 4.0 for morbidly obese women (BMI $>$ 35, 14%]. Similarly increased risk for hypertension, pre-eclampsia, fetal macrosomia ($>$ 4 kg birth weight) and cesarean section rate was found with obesity (Weiss et al., 2004). A similar pattern of significantly increased risk of the complications of pregnancy is found in the UK for the 15–20% of women entering pregnancy with obesity (BMI $>$ 30 kg/m^2) (Norman and Reynolds, 2011).

3.1.1. Maternal obesity programs offspring obesity

It is clear, from both human and animal studies, that obesity in pregnancy predisposes the offspring to obesity (Bayol et al., 2008; Chen et al., 2009; Godfrey et al., 2017), and through such early-life programming leads to a vicious trans-generational cycle (Ribaroff et al., 2017). Moreover, obesity in early pregnancy is associated with delays in post-natal neurodevelopment, tested at age 3.5 years (Girchenko et al., 2018). Intervention in the form of specialist advice at an early stage of pregnancy can improve the outcome in terms of increased numbers of live births and reduction in birth weight (Denison et al., 2017). While weight gain is a normal allostatic adjustment in pregnancy, there is an inverse relationship between initial BMI and total pregnancy weight gain (Patchen et al., 2016), perhaps indicating interaction between allostatic adjustments to obesity and to pregnancy (see Section 3.5). Also, women who exceed the recommended pregnancy weight gain retain ca. 3 kg more weight 3 years later than those who kept within the limits (Nehring et al., 2011): this may be considered as post-partum failure to correct this component of pregnancy allostatic load. Such a situation may be described as homeostatic overload by the reactive scope model of modified allostasis (Romero et al., 2009).

The important health problem of obesity in pregnancy is challenging to treat and would clearly be best managed by preventing early life and adolescent obesity: thus better preparing the 'pre-maternal brain' to engage healthy eating.

3.2. Inflammation, obesity and pregnancy

As emphasised by Power and Schulkin adipose tissue, like the placenta, secretes several hormones or humoral factors (e.g. leptin, cytokines/adipokines, steroids), and in pregnancy in an obese female their interactions are likely to be complex, involving management by the maternal brain (Power and Schulkin, 2012). In particular, obesity can be considered as an inflammatory state through production of adipokines by fat stores (Kershaw and Flier, 2004; Fain, 2006), and so can pregnancy itself as cytokines are produced by the placenta (Denison et al., 2010).

As discussed below (Sections 3.3.1–3.3.3), obesity involves inflammation in the brain, especially affecting appetite-regulating circuitry, in rats, mice and humans. It is not yet clear whether pregnancy, with or without obesity has such inflammatory effects in the brain.

3.3. Obesity-paradigm shift

In the past 20 years neuronal networks in the hypothalamus and brainstem that receive metabolic signals from the periphery and organise appropriate regulation of food intake and metabolism, mainly through neuropeptide signalling, have been extensively characterised (Schwartz et al., 2000; Yeo and Heisler, 2012). The arcuate nucleus in the mediobasal hypothalamus is the major portal, at the heart of the brain's networks for receiving metabolic signals and for regulating appetite and metabolism. The arcuate nucleus is the location of the neuropeptide Y (NPY)/agouti-related peptide (AGRP) and pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons that are primary regulators of appetite and metabolism (Schwartz et al., 2000). This foundation has provided a basis for investigating abnormalities in metabolic regulation in terms of altered balances in the activities of neurons in these networks: including allostatic changes in pregnancy (Russell and Brunton, 2014).

A basic concept is that in pregnancy effectiveness of signals that indicate hunger are increased, while effectiveness of satiety signals is decreased, through reduced production, or 'resistance' to their effects. Regarding orexigenic signals, some studies have found increased activity in pregnancy of neurons in the arcuate nucleus producing NPY (a potent centrally acting orexigen) (Ladyman et al., 2009; Trujillo et al., 2011). However, more emphasis is placed on resistance to, or reduced production of anorexic signals, in the endocrine environment of pregnancy: e.g. α-melanocyte stimulating hormone (α-MSH), from arcuate POMC neurons (Ladyman et al., 2009; Trujillo et al., 2011).

In the last ten years the paradigm has undergone major modification following the discovery of glial activation in the arcuate nucleus in response to an obesogenic diet, and their consequent role in obesity (Horvath et al., 2010). These changes are interpreted as both pathological and physiological, i.e. damaging and modifying activity of neurons in the arcuate nucleus (Chowen et al., 2018).

3.3.1. Gliosis and obesity

Here, we consider possible implications of this paradigm shift for understanding changes in metabolic control in pregnancy. High fat diet reduces neurogenesis in the arcuate nucleus, involving a reduction in the number of progenitor glial cells (McNay et al., 2012). The arcuate nucleus includes a stable population of microglia and astrocytes, and is adjacent to the tanycytes at the base of the third ventricle (Kalin et al., 2015). A hypercaloric environment activates these cells (De Souza et al., 2005), with cytokine production by microglia, which are also phagocytic and may be involved in neurite pruning (Kalin et al., 2015). In male mice, glial activation is rapidly stimulated by starting a high fat diet, and this is sustained in the consequent diet-induced obesity (Thaler et al., 2012); while activity of POMC neurons, inhibitors of appetite, is decreased (Moraes et al., 2009). Indeed these neurons show clear signs of injury and eventually reduced numbers (Thaler et al., 2012). The microglial responses indicate innate immune system activation with obesity and involvement in the regulation of energy metabolism (Kalin et al., 2015). It is evident that the microglial inflammatory signalling response to a high fat diet is an essential link between overconsumption and dysfunction of the regulatory neurons in the mediobasal hypothalamus, causing leptin resistance and diet induced obesity (Valdearcos et al., 2014, 2017). Leptin resistance in the arcuate nucleus, revealed as reduced phosphorylated signal transducer and activator of transcription-3 (pSTAT3) immunoreactive cells after

i.p. leptin injection, is seen 24 h after the start of a high fat diet, but over the following days there is a temporal pattern of partial recovery (Rizwan et al., 2017).

3.3.2. Sex differences

By contrast, female mice do not show gliosis with a high fat diet and are resistant to developing metabolic complications of diet-induced obesity, and indeed develop diet-induced obesity more slowly (Nickelson et al., 2012; Pettersson et al., 2012; Morselli et al., 2014; Gelineau et al., 2017). The lack of gliosis is due to estradiol actions on estrogen receptor-α (ERα) expressed in astroglia, which are positively regulated by peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (Pgc1α), which is in turn negatively regulated by high fat diet (Morselli et al., 2014). There is also a sex difference in microglia, which do not express ERα (Morselli et al., 2014), such that signalling in microglia of fractalkine (CX3CL1; a cytokine) to its receptor, CX3CR1, is greater in females (Dorfman et al., 2017). Microglia from rats also show sex differences in responses to stimulation (Yanguas-Casas et al., 2018).

Nonetheless, although less prone to develop obesity on a high fat diet than males (Chowen et al., 2018), female rats will become obese on a high fat diet, and sustain a pregnancy (Teo et al., 2017).

3.3.3. Astrocytes

Astrocytes are involved in glucose metabolism to support neurons, but with a high fat diet they can use fatty acids (Yi et al., 2011). Like microglia they react rapidly to a high fat diet (Thaler et al., 2012), and this astrocytosis interferes with, or filters neuronal responses to feedback signals, contributing to leptin resistance (Horvath et al., 2010; Chowen et al., 2016). However, the astroglial response to acute exposure to a high fat diet is important in restraining the immediate hyperphagic response (Buckman et al., 2015). Astrocytes are activated by palmitic acid, which is present in the circulation and brain in increased amounts with a high fat diet, and there are sex differences in this astroglial response (Morselli et al., 2014). It has been suggested that gliosis in the mediobasal hypothalamus in obesity might, through cytokine actions cause mitochondrial-endoplasmic reticulum dysfunction and leptin resistance in appetite-regulating neurons (Kalin et al., 2015).

As diet-induced obesity induces changes in the brain, specifically in the arcuate nucleus, that have been considered to indicate neuronal damage (Horvath et al., 2010), and interfere with normal homeostatic control of appetite and metabolism, this impact has to be considered as allostatic load, but with dysregulation of homeostatic mechanisms and damaging consequences (e.g. inflammation, insulin resistance). This is allostasis type 1 as defined by McEwen and Wingfield (McEwen and Wingfield, 2003). Nonetheless, arcuate nucleus inflammation subsides on returning (after 16 weeks) to normal diet (for 4 weeks) (Berkseth et al., 2014).

This perspective is of interest in the context of this review for two main reasons. First, is that in pregnancy, appetite and food intake are increased, and this resetting of control mechanisms (Russell and Brunton, 2014) i.e. metabolic allostasis, contributes to the allostatic load of pregnancy. Second, is the question of how the two states, of increased food intake and adiposity in pregnancy and the effects of diet-induced obesity in the pre-maternal brain, may interact in the maternal mediobasal hypothalamus. Furthermore, as obesity and chronic social stress may occur together, interactions between obesity and stress in pregnancy are a concern.

So far, it has been found that in women pregnancy increases basal maternal ACTH and glucocorticoid levels, and that obesity in pregnancy is associated with decreased pulsatile interstitial fluid glucocorticoid, but not ACTH levels (Stirrat et al., 2018). These findings indicate that an interaction between diet-induced obesity and HPA axis adaptations in pregnancy could be studied in a rodent model.

3.4. Metabolic allostasis in pregnancy

3.4.1. Offspring obesity programming

In a rat model of maternal obesity at the start of pregnancy, due to imposed over-nutrition for three weeks before mating, pregnancy proceeds normally with normal additional weight gain. Offspring were fostered onto normal mothers, but as adults the males showed an exaggerated propensity to develop obesity on a high fat diet. Hence, the maternal internal milieu from the start of pregnancy in an already obese female programmes an obese offspring phenotype (Shankar et al., 2008). Many studies, predominantly in rats and mice, have shown that a high fat diet in pregnancy, continuing into lactation, impacts adversely on metabolic control in later life in male and female offspring, with some sex differences (for a meta-review of 171 papers, see (Ribaroff et al., 2017; Chowen et al., 2018).

The adjustments in pregnant women can involve allostasis error, which may explain loss of control of eating in pregnancy, akin to binge eating, seen in 36% of a cohort of 11,132 women (vs 9–30% in the community) (Micali et al., 2018). Pregnancy weight gain in a subgroup with frequent loss of control (5%) was ca 3.7 kg more than normal, or as recommended. Notably, adverse programming of their offspring was indicated as at 15.5 years (n = 3779) they were more likely to be obese (Micali et al., 2018).

3.4.2. Resistance to anorexic signalling in pregnancy

3.4.2.1. Leptin resistance. It is not clear whether changes in glial activity in the mediobasal hypothalamus occur in pregnancy without or with additional diet-induced obesity. Current explanations for increased appetite and food intake in pregnancy involve resistance to satiety signals, particularly inhibitory central actions of leptin, although more is produced by the increasing adipose mass (and placenta in some species) in pregnancy (Ladyman and Grattan, 2004; Ladyman et al., 2012). This resistance involves decreased leptin receptor expression and reduced stimulation of pSTAT3 by leptin in the ventromedial nucleus (VMN), which regulates satiety (Ladyman and Grattan, 2005), without impairment of expression of genes important for metabolic regulation (Phillipps et al., 2013). By contrast, in the arcuate nucleus, the pSTAT3 response to leptin in POMC neurons, identified by α-MSH immunoreactivity, is maintained in pregnancy (Ladyman et al., 2009, 2012). Leptin resistance evidently involves central actions of prolactin, which has cytokine properties and is produced in increasing amounts through pregnancy, initially from the anterior pituitary, and later in the form of placental lactogen I and subsequently placental lactogen II (Naef and Woodside, 2007; Augustine and Grattan, 2008; Ladyman et al., 2010). It seems clear that these increased levels of prolactin drive increased food intake, though not via actions in the arcuate nucleus. Prolactin has been shown to reduce leptin transfer across the blood-brain barrier *in vitro* (Trujillo et al., 2011). However, there are reports of decreased *Pomc* and increased *Npy* mRNA expression in the arcuate nucleus in pregnancy (Ladyman et al., 2010; Trujillo et al., 2011; Martinez de Morentin et al., 2015). Whether or not prolactin (and normal changes in other endogenous hormones of pregnancy) has actions on glia in the mediobasal hypothalamus like those of diet-induced obesity without pregnancy is an unanswered question.

3.4.2.2. Central insulin resistance. Secretion of insulin in pregnancy is increased, and peripheral insulin resistance and raised blood glucose levels are evident, potentially leading to gestational diabetes mellitus as discussed in Section 3.1 (Power and Schulkin, 2012). Increased capacity for insulin secretion in pregnancy is a result of lactogenic hormone stimulation of pancreatic islet β-cell proliferation, mediated by prolactin receptors, which can be regarded as an allostatic mechanism (Banerjee et al., 2016). Hence, in mice conditional knockout of prolactin receptor expression in β-cells leads to gestational diabetes mellitus (Banerjee et al., 2016). Insulin also has central anorexic actions, signalling adequate energy supply, but in

pregnancy there is resistance to these actions. This is attributable to reduced responses of signalling mechanisms as phosphorylation of protein kinase B (Akt), in insulin target neurons in the arcuate and VMN, is lower in pregnant than non-pregnant rats after feeding or i.c.v. insulin infusion (Ladyman and Grattan, 2017). Conversely, phosphatase and tensin homologue (PTEN) is a negative regulator of insulin signalling, and decreased phosphorylated PTEN (P-PTEN, the less active form) in the VMN has been interpreted as indicating prolonged PTEN action against insulin signalling in pregnancy (Ladyman and Grattan, 2017). Mechanisms underpinning these allostatic molecular adaptations in pregnancy are not yet clear.

3.4.2.3. Resistance of oxytocin neurons. Oxytocin neurons exemplify resistance to feeding-related signals in one node in the appetite regulating circuitry in pregnancy. Activation of oxytocin neurons by food intake may, through actions of oxytocin secreted from the posterior pituitary on the heart, stimulate atrial natriuretic peptide (ANP) secretion and thus natriuresis to excrete an ingested salt load (Brunton et al., 2008a). Without pregnancy, oxytocin neurons are stimulated by central administration of the orexigen, NPY (Brunton et al., 2006a); as well as by circulating cholecystokinin (CCK) and secretin (which, acting via the vagus and nucleus tractus solitarii (NTS) indicate a recent meal) (Velmurugan et al., 2010), and by leptin (Velmurugan et al., 2013). These actions can be related to anticipation of eating or activation of digestion, or deposition of adipose, respectively. In pregnancy, oxytocin neurons show reduced activation by these stimuli (Fig. 1a), which for leptin, is contingent upon recent fasting (Brunton et al., 2008a; Velmurugan et al., 2013).

In the context of anorectic actions of oxytocin in the brain, it is considered that the source of this oxytocin is the dendrites of the magnocellular supraoptic (SON) and paraventricular nucleus (PVN) neurons (Sabatier et al., 2013), while oxytocin does not enter the brain from blood (Coombes et al., 1991; Leng and Ludwig, 2015). *Npy* gene expression in the arcuate nucleus is increased in pregnancy (Ladyman et al., 2009), yet oxytocin neuron responses to i.c.v. NPY are reduced in pregnancy (Brunton et al., 2006a). This results from activation of a central endogenous opioid mechanism as naloxone, an opioid antagonist, restores oxytocin secretory responses in pregnancy (Bales et al., 2006). The same opioid-mediated inhibition has been found for i.v. CCK action on oxytocin neurons (Douglas et al., 1995). Moreover, CCK is less effective in up-regulating Fos expression in NTS neurons in pregnancy (Ladyman et al., 2011).

Given by i.c.v. injection, α-MSH, a satiety peptide from POMC neurons, fails to suppress food intake in pregnancy (Ladyman et al., 2009), and actions on key hypothalamic neurons involved in satiety, including oxytocin neurons, are lost in pregnancy (Ladyman et al., 2016). Hence, increased nutrient intake in pregnancy may result from reduced satiety signalling in the hypothalamus, reducing activity of oxytocin neurons, among others. The involvement of glia in the mediobasal hypothalamus in these allostatic changes in pregnancy is presently unclear.

3.4.2.4. Fatty acid metabolism signalling. Another way in which appetite is stimulated, and thermogenesis (by brown adipose tissue) is reduced, has been revealed by finding reduced fatty acid metabolism in the rat hypothalamus in pregnancy (days 16–17), which in the non-pregnant state indicates energy abundance and reduces food intake and stimulates thermogenesis (Martinez de Morentin et al., 2015). This does not happen in pregnancy, indicating resistance to these changes in fatty acid metabolism. Malonyl-coenzyme A (malonyl-CoA) concentration in the hypothalamus is strongly increased, reflecting decreased levels (specifically in the ventromedial hypothalamus) of phosphorylated kinases involved in fatty acid synthesis and mRNA and protein levels of fatty acid synthase. Hence, in late pregnancy there is resistance to the anorectic effects of malonyl-CoA, which may involve reduced activity of the POMC neurons; otherwise the resistance mechanisms are not clear. The increasing levels of estrogen in late pregnancy are responsible for the hypothalamic profile of fatty acid metabolism in pregnancy (Martinez de Morentin et al., 2015).

Thus central resistance to leptin, signalling increased peripheral fat stores, is evidently supported by resistance to intra-hypothalamic signals of abundant fatty acid supply, together allowing increased appetite and food intake. This is a clear example of mechanisms of allostasis in pregnancy.

3.5. Interactions between metabolic allostasis and diet-induced obesity

Increased food intake and adiposity in pregnancy and diet-induced obesity may interact in the maternal mediobasal hypothalamus: i.e. is there occlusion, addition or synergism between these two allostatic loads, and are the mechanisms independent? An issue identified above (Section 3.4.2.4) (Martinez de Morentin et al., 2015) is what impact a high fat diet might have on this mechanism of resistance to anorectic signals in the hypothalamus from fatty acid metabolism?

It is clear that offspring from a pregnancy during which the mother has diet-induced obesity are programmed by their prenatal environment to be prone to develop obesity, and other metabolic disturbances (Ribaroff et al., 2017; Chowen et al., 2018). Moreover, maternal obesity induced by high fat diet during pregnancy leads to astrocytosis, likely due to IL-6 action, in the arcuate nucleus in fetal brains and in young neonates (Kim et al., 2016).

Understanding the mechanisms of dysfunction of the mediobasal

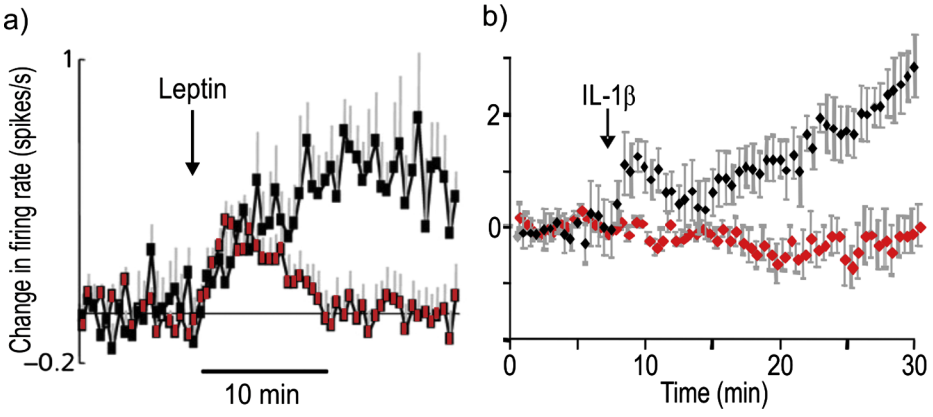

Fig. 1. Resistance of oxytocin neurons to stimulation by leptin or interleukin-1β in pregnancy: exemplifying allostasis in a neuroendocrine system. The mean change in firing rate (from baseline activity) ± SEM of oxytocin neurons in the supraoptic nucleus in response to (a) systemic leptin (100 μg i.v.); and (b) interleukin-1β (IL-1β; 500 ng/kg i.v.) in virgin (black symbols) and late (day 19–21) pregnant rats (red symbols). In late pregnancy, oxytocin neurons display resistance to activation by these stimuli, exemplifying changes in other components of neural networks regulating appetite and HPA axis responsivity in pregnancy, and indicative of allostasis. Data are adapted with permission from (Brunton et al., 2006b; Velmurugan et al., 2013). Licence numbers: 4462600523871; 4462600985833. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

hypothalamus of the maternal brain in pregnancy that lead to obesity and, in women, to overgrown offspring at birth, with a predictably shortened lifespan (Reynolds et al., 2013; Godfrey et al., 2017), is urgently needed to inform rational management.

Metformin treatment (to increase insulin sensitivity) in pregnancy has been trialled in obese women without gestational diabetes mellitus, and while it reduced maternal weight gain it does not impact birth weight, so is not recommended (Chiswick et al., 2015; Syngelaki et al., 2016). Potentially useful dietary supplementation in pregnancy with obesity is indicated by finding that resveratrol (a natural anti-oxidant) treatment of pregnant rats can attenuate the effects of high fat diet on the offspring (Ros et al., 2018).

3.5.1. Leptin signalling

A way forward is to investigate the consequences of abolishing leptin signalling in pregnancy in key neurons. Among 10 genes related to leptin biology, only suppressor of cytokine signalling-3 (*Socs3*) and the leptin receptor (LepR; *Lepr*) genes show up-regulation in the mouse hypothalamus in pregnancy (Zampieri et al., 2015). *Socs3* is increased in the hypothalamus of obese Agouti mice, and is recognised as a mediator of leptin resistance (Bjorbaek et al., 1998, 1999). Mice lacking *Socs3* in only cells expressing LepR have been produced and used to test a role in leptin resistance in pregnancy (Zampieri et al., 2015). Such mice do not show increased hypothalamic *Socs3* expression in pregnancy, so in normal mice this must be in cells expressing LepR, and leptin stimulates an exaggerated pSTAT3 response in *Socs3* knockout cells, indicating an inhibitory role of Socs3 in normal LepR cells (Zampieri et al., 2015). In pregnancy, these knockout mice eat less, gain less weight and deposit less adipose tissue than pregnant controls, but adiposity is like that in virgins. Otherwise pregnancy in the *Socs3* knockout mice was essentially normal; however, they have low leptin levels, lack leptin resistance, but rather show enhanced hypothalamic leptin sensitivity, and do not show insulin resistance, so are protected from gestational diabetes mellitus (Zampieri et al., 2015). However, offspring of mothers with *Socs3* knockout in LepR-expressing cells are abnormal: they have slower growth initially, reduced brain size as adults, and changes in appetite-regulating circuitry in the hypothalamus (Ramos-Lobo et al., 2018). Clearly, the allostatic load on the pregnant mother from ensuring the needs of fetuses and offspring has a cost for her, but does have essential benefits for the offspring.

Knockout of *Socs3* from LepR-expressing cells does not prevent diet-induced obesity without pregnancy, although insulin resistance is improved (Pedroso et al., 2014). Evidently, SOCS3 is not a therapeutic target for managing diet-induced obesity. The question arises about what the phenotype would be in a mouse with *Socs3* knockout in LepR cells exposed to diet-induced obesity and pregnancy: would diet-induced obesity, and effects on the offspring be mitigated?

4. Stress in pregnancy: mother

4.1. Allostatic changes in neuroendocrine responses to stress

Adverse consequences for a female and offspring experiencing chronic stress before and during pregnancy are a concern, given that ca.10% of women worldwide report abuse during pregnancy (Russell and Brunton, 2008). Allostatic load indices from adverse circumstances before and continuing through pregnancy have been compiled, for use in assessing, for instance, the impact on pre-term birth (Olson et al., 2015). Allostatic mechanisms that reduce neuroendocrine stress responses are activated in pregnancy, which may mitigate effects of stress on the mother and fetus.

In a normal pregnancy the maternal HPA axis is less responsive to acute stressors, through activation of inhibitory mechanisms by hormones of pregnancy (Brunton and Russell, 2008, 2010a; Russell and Brunton, 2014), which can be considered as an allostatic change. Hence, allostasis can involve *reduced* activity of some systems, but nonetheless at a cost: e.g. in pregnancy reduced defence capability against challenges usually mediated by increased HPA axis activity (Dhabhar, 2018).

Following studies that showed reduced HPA axis stress responses in lactation (Windle et al., 1997), we sought precursor changes at the end of pregnancy in expression of genes in the PVN with a key role in the regulation of the HPA axis. We found decreased *Crh* mRNA expression in the PVN at the end of pregnancy and through parturition, with no change in proenkephalin-A (pENK-A; *Penk*) or oxytocin (*Oxt*) mRNA expression (Douglas and Russell, 1994). This led us to investigate further the impact of pregnancy on HPA axis function, guided by studies on oxytocin neurons.

4.2. Oxytocin neurons

Allostatic changes, or plasticity, in the magnocellular oxytocin system in pregnancy provided guidance for analysing HPA axis changes in pregnancy. Magnocellular oxytocin neurons also respond to stressors (Lang et al., 1983; Onaka, 2000), and previous studies have revealed powerful inhibitory actions of endogenous opioid peptides and μ- and κ-opioid receptor selective opiates (Russell et al., 1989; Douglas et al., 1993a). In particular, studies in pregnancy showed important roles for endogenous opioid peptides in restraining the activity of oxytocin neurons. Hence, progress of parturition can be suspended, in rats and pigs, in response to an environmental stressor (Leng et al., 1987; Lawrence et al., 1994). This involves reduced oxytocin secretion owing to activation of endogenous opioid mechanisms as naloxone (a potent opioid antagonist) reverses the suspension of births (Leng et al., 1987; Lawrence et al., 1992). Actually, endogenous opioid restraint of oxytocin secretion in parturition is an important governing mechanism as naloxone treatment increases oxytocin secretion and speeds up births, which is deleterious (Leng et al., 1988).

4.2.1. Central opioid actions on oxytocin neurons

While opioid release and action, especially via κ-opioid receptors in the posterior pituitary is important during pregnancy, effectiveness of this mechanism fades towards the end of pregnancy (Sumner et al., 1992; Douglas et al., 1993b), leaving a central μ-opioid mechanism predominant, associated with reduced μ-opioid receptor binding in the SON (Sumner et al., 1992). The origin of the endogenous opioids that can act in the SON may be the POMC neurons in the arcuate nucleus, as direct projections from β-endorphin-containing neurons into the SON have been shown (Douglas et al., 2002). The number of arcuate neurons expressing *Pomc* mRNA increases in pregnancy, but they are not activated at parturition, and activation by stress remains to be demonstrated (Douglas et al., 2002).

The most impressive opioid effect on oxytocin neurons is induction of morphine dependence which is seen after i.c.v. infusion for five days as a profound and long-lasting excitation of the electrical and secretory activity of the oxytocin neurons, precipitated by naloxone injection (Pumford et al., 1991). There may be a milder physiological equivalent of endogenous opioid dependence at the end of pregnancy, with reduced central endogenous opioid action contributing to increased oxytocin secretion for parturition. Evidence for this is that near the end of pregnancy (but not earlier or in virgin rats), naloxone increases oxytocin secretion into the blood, stimulates Fos expression in the oxytocin neurons, stimulates oxytocin release within the SON and enhances electrical excitation by i.v. CCK (Douglas et al., 1995). As norbinaltorphine, a κ-opioid antagonist, has no such effects it was inferred that central opioid restraint of oxytocin neurons in late pregnancy is via μ-opioid receptors (Douglas et al., 1995).

4.2.2. Nitric oxide

Production of nitric oxide by oxytocin neurons via neuronal nitric oxide synthase (nNOS; *Nos1*) provides a tonic auto-inhibitory mechanism which reduces, for example, the effectiveness of hyperosmotic

stimulation. This mechanism is strongly down-regulated at the end of pregnancy, through an allostatic reduction in the expression of *Nos1* mRNA in oxytocin neurons, which is considered to increase oxytocin neuronal excitability and enhance the capacity for oxytocin secretion in parturition (Srisawat et al., 2000).

4.3. Reduced neuroendocrine stress responses in pregnancy

As mentioned in Section 4.1, in seeking origins of the central endogenous opioid inhibition, we measured *Penk* gene expression in the medial parvocellular PVN (mpPVN): despite finding no change in *Penk* mRNA expression, there is significantly reduced *Crh* mRNA expression in the PVN (Douglas and Russell, 1994).

Reduced oxytocin and HPA axis responses to stress (i.p. hypertonic saline injection) in lactation had been reported, and the effects shown to depend upon suckling (Lightman and Young, 1989). Reduced HPA axis responses to noise stress and to lipopolysaccharide injection were also found (Windle et al., 1997; Shanks et al., 1999), and reduced effectiveness of noradrenergic input to the PVN was implicated (Toufexis et al., 1998). Our finding of reduced *Crh* mRNA expression in the PVN in late pregnancy stimulated us to investigate the effects of stress on oxytocin neurons and the HPA axis in pregnancy, and a role for endogenous opioids and sex steroid hormones, altogether different from the suckling-dependent mechanisms in lactation (Brunton et al., 2008b).

Initially we used a combined physical and psychogenic stressor (forced swimming for 90 s): oxytocin secretion was increased by swimming in both virgin and day 21 pregnant rats, but naloxone pretreatment further increased oxytocin secretion to a greater extent in the pregnant compared with virgin rats, indicating greater endogenous opioid inhibition and enhanced underlying secretory capacity in pregnancy (Douglas et al., 1998). In contrast, ACTH and corticosterone secretion was increased less by swimming in pregnant rats (Fig. 2), but was increased after naloxone pre-treatment. Whereas naloxone decreased ACTH and corticosterone secretion stimulated by swim stress in virgin rats, indicating a stimulatory endogenous opioid tone, opposite to that in pregnancy (Douglas et al., 1998). Hence, endogenous opioid action inhibits oxytocin and ACTH and corticosterone secretory responses to swim stress in late pregnancy (Douglas et al., 1998).

4.3.1. Mechanisms of reduced HPA axis activity

Further studies showed that by the end of pregnancy in rats and mice, HPA axis responses to a range of physical and emotional stressors are substantially reduced (Fig. 2), and that this is due to reduced responsiveness in the neural circuitry in the brain controlling the axis (Johnstone et al., 2000; Douglas et al., 2003; Brunton, 2010). This hyporesponsiveness develops progressively in the last third of pregnancy (Johnstone et al., 2000) and persists during lactation (Windle et al., 1997; Neumann et al., 1998).

4.3.2. HPA axis negative feedback mechanisms

Negative feedback by glucocorticoid on the HPA axis is mediated via glucocorticoid (GR; *Nr3c1*) and mineralocorticoid receptors (MR; *Nr3c2*) at several levels. We found increased *Nr3c1* (but not *Nr3c2*) mRNA expression in the dentate gyrus, consistent with increased feedback at this level (Johnstone et al., 2000). 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) reactivates corticosterone from its inert metabolite (11-dehyrocorticosterone), and 11β-HSD1 enzyme activity in the PVN and anterior pituitary is increased in late pregnancy. However, i.c.v. infusion of glycyrrhetinic acid, an inhibitor of 11β-HSD1, does not alter the reduced HPA axis stress response in late pregnancy (Johnstone et al., 2000). After pharmacological suppression of glucocorticoid synthesis, to reduce feedback, acute corticosterone administration decreases ACTH secretion more slowly in pregnancy, indicating decreased, rather than increased rapid feedback sensitivity (Johnstone et al., 2000). Hence, overall, the proportionately reduced

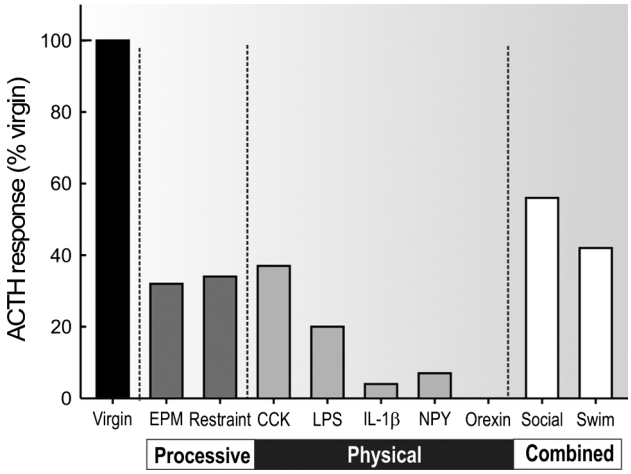

Fig. 2. Reduced HPA axis responses to different stressors in late pregnancy. Summary of peak ACTH responses during late pregnancy (day 20/21) following exposure to a variety of different processsive (or psychological), physical, or combined (processive and physical) stressors, expressed as a percentage of the response measured in virgin female rats. Abbreviations: CCK, cholecystokinin (20 μg/kg i.v.); EPM, elevated plus maze (5 min); LPS, lipopolysaccharide (endotoxin; 1 μg/kg i.v.); IL-1β, interleukin-1β (500 ng/kg i.v.); NPY, neuropeptide Y (5 μg i.c.v.); orexin, orexin-A (0.5 μg i.c.v.); swim, forced swimming (90 s); social, social stress induced by a resident-intruder paradigm (10 min). Reduced ACTH responses to IL-1β or forced swimming (90 s) in late pregnancy are reversed (not shown) by prior inhibition of 5α-reductase (with finasteride or 4-MA, respectively) to block allopregnanolone production. Naloxone prevents reduced responses to CCK and IL-1β (not shown), indicating inhibition by an endogenous opioid mechanism in late pregnancy. Hence an allopregnanolone-opioid mechanism causes allostatic reduction in HPA axis responses to stressors in pregnancy (see Fig. 3). Based on data from: (Neumann et al., 1998; Brunton et al., 2000, 2005, 2006a; Brunton and Russell, 2003, 2010b; Douglas et al., 2005).

Crh and *Avp* mRNA expression in the mpPVN in late pregnancy is deduced to result from reduced forward drive rather than enhanced glucocorticoid negative feedback.

4.3.3. Corticotrophs

Given reduced ACTH secretory responses to stressors in late pregnancy, we sought to differentiate underlying changes in arginine vasopressin (AVP) and CRH output from the hypothalamus and their actions on the anterior pituitary corticotrophs (Ma et al., 2005). Along with the reduced *Crh* mRNA content in the mpPVN in late pregnancy (Douglas and Russell, 1994), CRH peptide content in the median eminence is reduced by 12% near the end of pregnancy (Ma et al., 2005). Moreover, ACTH secretory responses to either intravenous CRH or AVP are reduced in late pregnancy by about 50% compared with virgins, yet the response to CRH and AVP given in combination is intact (Ma et al., 2005). Anterior pituitary CRH receptor-1 (CRH-R1; *Crhr1*) mRNA expression is not altered by pregnancy, and ACTH content is not reduced, despite reduced *Pomc* (ACTH precursor) mRNA expression (Ma et al., 2005). Furthermore, the CRH-R1 antagonist antalarmin (i.p.) reduces the ACTH response to forced swimming to a similar extent (around 50%) in virgin and late pregnant rats (Ma et al., 2005). Hence CRH secretion and action are not diminished in late pregnancy. Indeed, *in vitro* measurements of ACTH secretion from anterior pituitary cells indicate sensitivity to CRH is increased in late pregnancy, as is augmentation of CRH action by AVP, which is associated with enhanced cAMP action (Ma et al., 2005). For AVP actions, the findings are different: while a V1/V2 receptor antagonist given i.v. reduces, by around 50%, the ACTH response to forced swimming in virgin rats, it has no effect in late pregnant rats. This may reflect a 20% reduction in AVP receptor-1b (*Avpr1b*) mRNA expression in the anterior pituitary near the end of

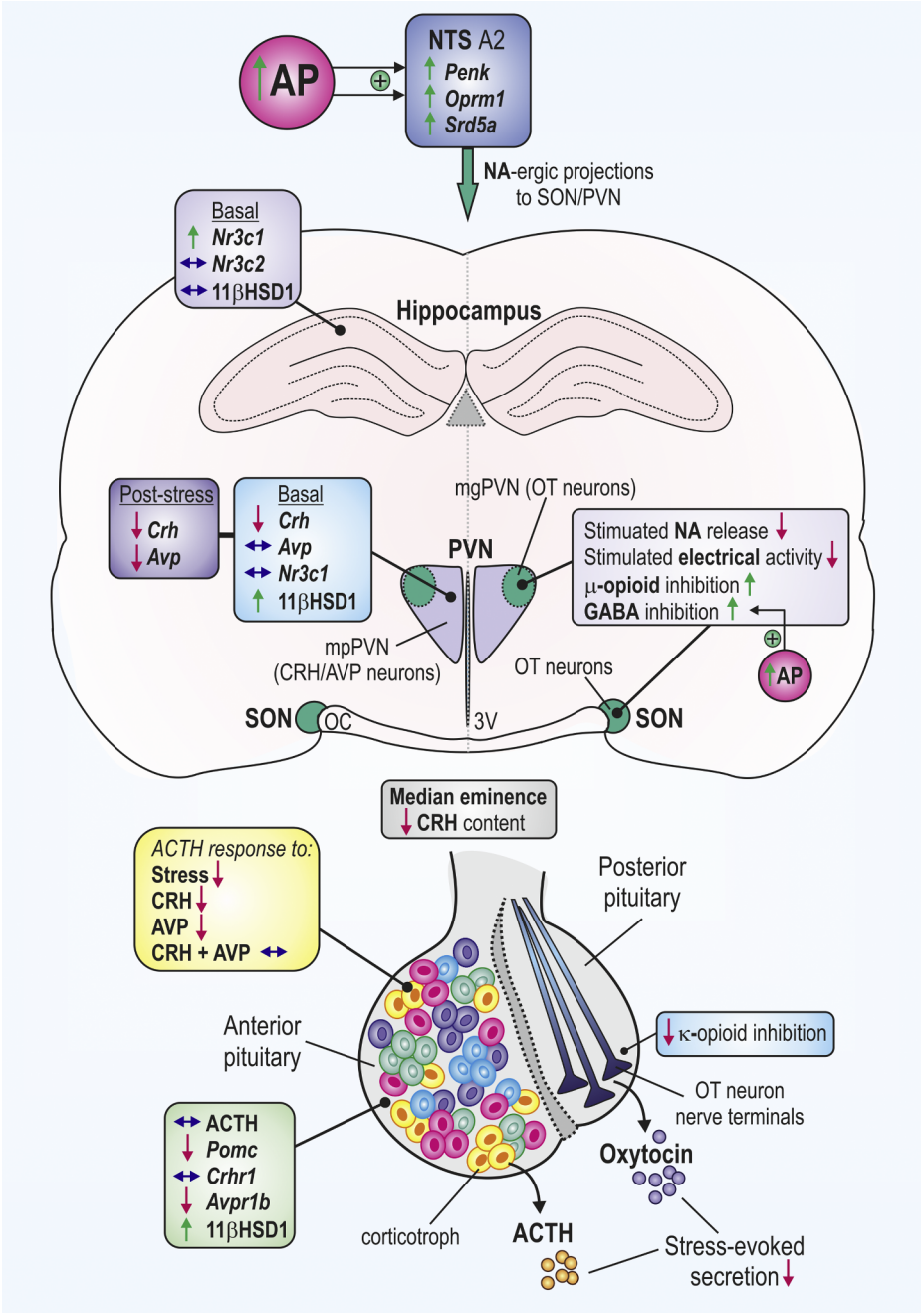

Fig. 3. Summary of the allostatic mechanisms reducing neuroendocrine responses to stress in late pregnancy. In late pregnancy, the HPA axis and oxytocin system are less responsive to stimulation by stress. This is associated with altered gene expression in the brain and the pituitary under basal and stress conditions. Green upward arrow indicates greater expression, red downward arrow indicates lower expression and blue double-ended horizontal arrow indicates no change in late (d20-21) pregnant rats relative to non-pregnant females. Under basal conditions, *Crh* expression in the mpPVN and *Pomc* expression in the anterior pituitary is lower in late pregnant rats. This may reflect enhanced glucocorticoid negative feedback since *Nr3c1* is up-regulated in the dentate gyrus of the hippocampus and activity of 11β-HSD1 is increased in the PVN and anterior pituitary, indicating increased local regeneration of glucocorticoid. In late pregnancy, the corticotrophs are less sensitive to stimulation by stress, CRH and AVP, reflected by lower levels of ACTH secretion; however the ACTH response to CRH and AVP given together is indistinguishable from that in virgin rats. Noradrenergic A2 neurons in the brainstem NTS project to CRH neurons in the mpPVN and to magnocellular oxytocin neurons in the SON and PVN. In non-pregnant rats, noradrenaline released in the SON and PVN (in response to stimulation by e.g. cholecystokinin, forced swimming or interleukin-1β) excites the CRH and oxytocin neurons, stimulating CRH release at the median eminence and oxytocin secretion from the posterior pituitary. In late pregnancy, systemic interleukin-1β and swim stress are less effective in evoking noradrenaline release from the terminals in the PVN; hence the CRH and oxytocin neurons are less strongly stimulated and subsequently ACTH and oxytocin secretion is markedly attenuated compared with virgin rats. This is evidently a result of increased opioid inhibition as naloxone restores HPA axis (up-regulates *Crh* in the PVN and increases ACTH and corticosterone secretion) and oxytocin responses (increases the firing rate of, and induces Fos in SON oxytocin neurons, and increases oxytocin secretion) in late pregnant rats. The proposed mechanism is enkephalin acting presynaptically on up-regulated μ-opioid receptors, presumptively on the noradrenergic nerve terminals in the SON/PVN. Increased levels of allopregnanolone (formed from high levels of progesterone) in the brain in late pregnancy up-regulate *Penk* and *Oprm1* gene expression in the NTS neurons. Increased *Srd5a* expression in the NTS in pregnancy is also expected to increase local allopregnanolone synthesis. Additionally, allopregnanolone also inhibits oxytocin neurons by positively modulating GABA inhibition in the SON/PVN via actions on $GABA_A$ receptors. Abbreviations: 3 V, 3rd ventricle; 11βHSD1, 11β-hydroxysteroid dehydrogenase-1; AP, allopregnanolone; AVP, arginine vasopressin; *Avpr1b*, AVP receptor 1b; CRH, corticotropin releasing hormone; *Crhr1*, CRH receptor-1; mgPVN, magnocellular paraventricular nucleus; mpPVN, medial parvocellular PVN; *Nr3c1*, glucocorticoid receptor; *Nr3c2*, mineralocorticoid receptor; NA, noradrenaline; NA-ergic, noradrenergic; NTS, nucleus tractus solitarii; OC, optic chiasm; *Oprm1*, μ-opioid receptor; OT, oxytocin; *Penk*, pro-enkephalin-A; *Pomc*, pro-opiomelanocortin; SON, supraoptic nucleus; *Srd5a*, 5α-reductase. Based on data from: (Douglas et al., 1993b, 1995, 2005; Concas et al., 1998; Brussaard and Herbison, 2000; Johnstone et al., 2000; Brunton et al., 2005, 2006b, 2009; Ma et al., 2005). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pregnancy, but as exogenous AVP administered together with CRH produces a full, virgin-like, ACTH response, we concluded that the reduced ACTH response to swim stress in late pregnancy reflects reduced secretion of AVP rather than CRH by mpPVN neurons (Ma et al., 2005).

Together, these results characterise a functional molecular signature for pregnancy allostasis at the level of the anterior pituitary corticotrophs (Fig. 3).

4.4. Feed-forward mechanisms

4.4.1. Oxytocin neurons

In the context of pregnancy and parturition, input to oxytocin neurons from the brainstem is of key importance in conveying neural signals from the birth canal that form the afferent limb of the Ferguson reflex; this is a positive feedback mechanism by which uterine contractions stimulated by oxytocin secreted during parturition further stimulate oxytocin neurons to promote births (Russell et al., 2003).

Spinal afferents relay in the NTS, and activate A1 and A2 catecholaminerigc neurons that project to the magnocellular oxytocin neurons (Meddle et al., 2000), with A2 noradrenergic neurons having a key role (Douglas et al., 2001). A2 noradrenergic neurons also mediate the excitatory actions of i.v. CCK on oxytocin neurons, and notably this input is inhibited by morphine acting presynaptically, by inhibiting noradrenaline release (Onaka et al., 1995a, 1995b).

4.4.1.1. Interleukin-1β. Further analysis of central mechanisms governing the magnocellular oxytocin neurons and HPA axis undergoing allostatic changes in pregnancy was pursued using an immune stressor as central pathways for this physical stressor had been characterised, and infection in pregnancy is a challenge (Hagberg et al., 2005). The catecholaminergic NTS neurons have a major role in signalling circulating interleukin-1β (IL-1β) actions to magnocellular oxytocin and mpPVN CRH neurons (Ericsson et al., 1994; Buller et al., 2001). A key site of initial action of IL-1β is the blood vessels supplying the NTS, which have interleukin receptors; these mediate activation of cyclo-oxygenase 2 (COX-2) for prostaglandin synthesis, and the generated prostaglandin E2 acts on prostaglandin receptors (EP4) on A2 noradrenergic neurons projecting to the PVN and SON (Rivest et al., 2000).

Oxytocin secretion is increased around 3-fold in virgin rats by i.v. IL-1β, following a sustained 34% increase in firing-rate of SON oxytocin neurons; by contrast, in late pregnant rats oxytocin neurons show no response to i.v. IL-1β (Brunton et al., 2006b) (Fig. 1b). However, i.v. naloxone administration rapidly restores the secretory and electrophysiological response of oxytocin neurons in pregnant rats; indeed, naloxone produces a greater secretory response than seen in virgin rats. Evidently, this is likely through reversal of presynaptic inhibition of noradrenaline release in the SON, by analogy with the PVN (see Section 4.4.2, (Brunton et al., 2005)) and morphine actions in the SON (Onaka et al., 1995b). The greater secretory response to IL-1β after naloxone in pregnant than in virgin rats is considered to reflect the larger oxytocin store in the posterior pituitary at the end of pregnancy (Douglas et al., 1993b).

4.4.2. HPA axis

In virgin rats i.v. injection of lipopolysaccharide (LPS, endotoxin) or IL-1β sequentially increases ACTH and corticosterone secretion, *Crh* mRNA expression in the mpPVN and *Pomc* mRNA expression in the anterior pituitary (Brunton et al., 2005). In striking contrast, there is no such activation of the HPA axis in late pregnant rats (Brunton et al., 2005). As Fos expression in NTS A2 neurons is similarly increased after i.v. IL-1β in virgin and late pregnant rats, it could be inferred that in pregnancy there is transmission failure of the IL-1β signal in the projection between the NTS and the mpPVN CRH neurons (Brunton et al., 2005). This was confirmed by showing with microdialysis of the PVN, and subsequent reverse phase HPLC and electrochemical detection measurements, that i.v. IL-1β increases noradrenaline release in the PVN in virgin rats, but fails to do this in late pregnant rats (Brunton et al., 2005). Moreover, in pregnant rats i.v. naloxone restores HPA axis activation by i.v. IL-1β, and naloxone microdialysed directly into the PVN restores noradrenaline release in response to systemic IL-1β. Hence local opioid action in the PVN in pregnancy inhibits noradrenaline release and HPA activation (Brunton et al., 2005), analogous to morphine action in the SON on oxytocin neurons mentioned in Section 4.4.1 (Onaka et al., 1995b).

The source of this opioid is evidently the NTS A2 neurons, as *Penk* mRNA expression here is increased near the end of pregnancy, while μ-opioid receptor (*Oprm1*) mRNA expression is also increased (Brunton et al., 2005). These findings led to the inference that an enkephalin, from the pENK-A precursor, and its receptor may be transported in the axons of A2 neurons to the mpPVN and effect pre-terminal inhibition of noradrenaline release in late pregnancy (Brunton et al., 2005).

Together, these studies describe components of an allostatic mechanism, involving activation of an opioid-mediated inhibitory mechanism in the brain that reduces magnocellular oxytocin neuron and HPA axis responsiveness in late pregnancy (Fig. 3).

4.4.3. Mice are different

HPA axis responses to a novel environment or forced swimming, measured as increased Nur77 (*Nr4a1*; immediate early gene) mRNA expression in the mpPVN and ACTH secretion in virgin mice, are absent in late pregnant mice; although basal plasma corticosterone concentrations are high in late pregnancy (Douglas et al., 2003). As naloxone has no effect on ACTH secretion in late pregnant mice, endogenous opioid inhibition is not responsible for the lack of central HPA axis drive in pregnancy in this species (Douglas et al., 2003).

4.4.4. Orexin and neuropeptide Y

Orexins are neuropeptides that have central arousal and orectic actions, but also activate the HPA axis (Edwards et al., 1999; Hagan et al., 1999; Al-Barazanji et al., 2001; Russell et al., 2001), which, through the energy mobilizing actions of glucocorticoids, can be considered to be consistent with the other actions of orexins. We showed that while i.c.v. injection of orexin-A stimulates the HPA axis in virgin rats it has no such actions in day 21 pregnant rats, as assessed by measurement of *Crh* mRNA expression in the mpPVN, and circulating ACTH and corticosterone concentrations (Brunton and Russell, 2003). Orexin-A may act indirectly on CRH neurons by stimulating arcuate NPY neurons (Russell et al., 2001). NPY given by i.c.v. infusion rapidly stimulates eating and the HPA axis, via activation of mpPVN CRH and AVP neurons, while also activating PVN and SON magnocellular oxytocin neurons (Brunton et al., 2006a). In late pregnancy these actions of NPY on the HPA axis and oxytocin neurons are not seen, but NTS neurons are activated as in virgins and the eating response is intact (Bales et al., 2006; Brunton et al., 2006a). Hence, resistance to NPY of the HPA axis and oxytocin neurons in late pregnancy can explain resistance to orexin-A.

In further experiments, involvement in pregnancy of opioid inhibition of NPY actions on the HPA axis was revealed by administering naloxone 30 min before i.c.v. NPY in late pregnant and virgin rats, and finding that NPY now increased *Avp* mRNA and Fos expression in the mpPVN in pregnant rats, while naloxone had no effects on NPY actions in virgins (Bales et al., 2006). Fos expression in NTS neurons in both late pregnant and virgin rats was increased by i.c.v. NPY without naloxone pre-treatment (Bales et al., 2006), so it could be that the endogenous opioid mechanism activated in the NTS in pregnancy, which evidently auto-inhibits noradrenaline release (Brunton et al., 2005), is also responsible for HPA axis resistance in pregnancy to NPY and orexin. However, the finding that naloxone reduced stimulation of Fos expression in NTS neurons by i.c.v. NPY in both late pregnant and virgin rats is unexplained (Bales et al., 2006).

The endogenous opioid-induced loss of orexin-A and NPY actions on the HPA axis and oxytocin neurons in pregnancy will favour energy conservation in pregnancy, and can be considered as an allostatic change.

4.5. Sex steroids

4.5.1. Opioid induction

To test whether levels of female sex steroids in pregnancy induce the opioid inhibition of the oxytocin system and the HPA axis, non-pregnant virgin rats were implanted with subcutaneous silastic capsules containing estradiol and progesterone for 16–17 days, with or without removal of the progesterone capsules to mimic the progesterone withdrawal seen at the end of pregnancy (Douglas et al., 2000; Russell and Brunton, 2014). Oxytocin secretion in response to swim stress was greater in the sex steroid treated rats after naloxone, indicating induction of opioid inhibition by the combined steroid treatment (Douglas et al., 2000). However, the HPA axis response was not altered

by this sex steroid regime (Douglas et al., 2000).

4.6. Progesterone and allopregnanolone

We sought expression of progesterone receptors in NTS neurons, and found neurons immunoreactive for tyrosine hydroxylase (the rate-limiting enzyme in catecholamine synthesis) only rarely co-express progesterone receptors, and there is no increase during pregnancy, despite increasing estrogen levels (Francis et al., 2002). This led us to consider actions of the progesterone neuroactive metabolite, allopregnanolone (3α-hydroxy-5α-pregnan-20-one), which has neuronal membrane actions. In particular, allopregnanolone acts as an allosteric modifier at $GABA_A$ receptors, enhancing inhibitory actions of GABA (Concas et al., 1998), including on oxytocin neurons at the end of pregnancy (Brussaard and Herbison, 2000). Moreover, allopregnanolone has similar allosteric inhibitory actions on the activity of CRH neurons (Gunn et al., 2011, 2015).

Like progesterone, allopregnanolone is present at high concentrations in pregnancy in the periphery and in the brain (Concas et al., 1998). Allopregnanolone is synthesised from progesterone via dihydroprogesterone by the actions of 5α-reductase (*Srd5a*; the rate-limiting enzyme) and 3α-hydroxysteroid dehydrogenase (3αHSD; *Akr1c4*) (Do Rego et al., 2009); both of which are expressed in the brain (Jung-Testas et al., 1989; Krieger and Scott, 1989; Melcangi et al., 1993), with glia and neurons co-operating in the production of allopregnanolone (Gunn et al., 2015). Hence inhibitors of 5α-reductase provide a tool to suppress production of allopregnanolone to investigate its functions. We showed that the activity of 5α-reductase and 3α-HSD in the hypothalamus, and mRNA expression of their genes in the PVN and NTS are increased in late pregnancy, indicating the possibility for neuroactive steroid production at both locations to influence CRH and oxytocin neurons directly or via the NTS input (Brunton et al., 2005).

4.6.1. Allopregnanolone and the HPA axis

Initially, we examined a role in late pregnancy for inhibition by endogenous allopregnanolone of HPA axis responses to forced swimming for 90 s. Late pregnant and virgin rats were given s.c. injections (33 mg/kg) of 17beta-N, N-diethylcarbomyl-4-aza-4-methyl-5alpha-androstan-3-one (4-MA), a 5α-reductase inhibitor, or vehicle 16 h and 1.5 h before the swim (Ma et al., 2002). The increase in ACTH concentration at 5 min after swimming was 1.5-fold greater in untreated virgins compared with pregnant rats. 4-MA pre-treatment did not affect the ACTH increase in virgin rats, but increased the response in the pregnant rats to the virgin level; consistent with a loss of inhibitory action of endogenous allopregnanolone on the initial central response (Ma et al., 2002). Interestingly, 4-MA prolonged the ACTH response in both virgin and pregnant rats, so that levels were ca. 4.5-fold greater than vehicle-treated rat levels 70 min after swimming (Ma et al., 2002); this finding indicates prevention of central 5α,3α-tetrahydrodeoxycorticosterone (5α,3α-THDOC) synthesis by 4-MA and hence reduced post-stress negative feedback inhibition of the HPA axis (Purdy et al., 1991), although effects on CRH neurons are complex (Sarkar et al., 2011).

4.6.2. Allopregnanolone and opioid restraint of HPA axis

We tested the hypothesis that in late pregnancy allopregnanolone, acting in the brain, inhibits HPA axis responses to systemic IL-1β, and does so by inducing the expression of the endogenous opioid mechanism in the NTS that we had shown prevents the HPA axis from responding, described in Section 4.4.2 (Brunton et al., 2005). To block allopregnanolone synthesis, rats in late pregnancy were given two injections of either vehicle or finasteride (a 5α-reductase inhibitor), 20 and 2 h before challenge with i.v. IL-1β (Brunton et al., 2009). This finasteride treatment restored all HPA axis responses to IL-1β, as seen in virgin rats: i.e. increased mpPVN *Crh* mRNA expression, ACTH and corticosterone secretion. Conversely, allopregnanolone injections on the same schedule in virgin rats reduced HPA axis responses (Brunton et al., 2009). While naloxone reversed the suppressed HPA axis responses to IL-1β in late pregnant rats, as expected, naloxone had no additional effects to those of finasteride in restoring HPA responses (Brunton et al., 2009). Hence, it was inferred that allopregnanolone induces opioid inhibition of the HPA axis in pregnancy (Brunton et al., 2009). Indeed, finasteride treatment reduced the raised expression of *Penk* mRNA in the NTS in late pregnant rats; while further experiments involving allopregnanolone and naloxone treatment of virgin rats showed allopregnanolone induces opioid inhibition of the HPA axis as in pregnancy, and increases *Penk* mRNA expression in the NTS (Brunton et al., 2009).

How allopregnanolone regulates *Penk* mRNA expression is not clear. Nonetheless, the central allopregnanolone-endogenous opioid link in pregnancy provides an allostatic mechanism for reducing HPA axis responsiveness to stressors in late pregnancy (Fig. 3).

4.6.3. Social stress

We have shown that HPA secretory responses to repeated social stress in late pregnancy are also significantly reduced (Brunton and Russell, 2010b). We had anticipated that the mechanisms that reduce HPA axis responses would confer protection for fetuses against adverse programing *in utero* (Brunton and Russell, 2011). However, this was found not to be the case, and instead enabled us to establish, without interfering with the mechanisms restraining the maternal HPA axis, a model of prenatal programming by maternal exposure to social stress (Brunton and Russell, 2010b) as reviewed in Section 6. Consequently, we have not yet investigated whether the allopregnanolone-opioid mechanism described above underlies the reduced maternal HPA responsiveness to repeated social stress in pregnancy.

4.6.4. Allopregnanolone and oxytocin neurons

Essentially, the allopregnanolone-opioid mechanism (Brunton and Russell, 2010a) discussed for the HPA axis in Section 4.6.2 also restricts responses of the magnocellular oxytocin system to stressors in late pregnancy (Fig. 3). As described in Section 4.4.1, we showed that electrophysiological and secretory responses of oxytocin neurons to i.v. IL-1β are inhibited by an endogenous opioid peptide mechanism in late pregnancy (Brunton et al., 2006b). Allopregnanolone is importantly involved in the suppressed oxytocin responses to i.v. IL-1β as finasteride treatment across 20 h before i.v. IL-1β injection restores an oxytocin secretory response in late pregnant rats, and allopregnanolone treatment together with finasteride suppresses the response (Brunton et al., 2012). Naloxone and finasteride effects are not additive, whereas naloxone alone also restores the response, indicating, as for the HPA axis that allopregnanolone induces endogenous opioid inhibition of oxytocin neurons (Brunton et al., 2012). Finasteride action is central as it restores Fos expression in PVN and SON oxytocin neurons in response to i.v. IL-1β (Brunton et al., 2012). Conversely, allopregnanolone treatment of virgin rats suppresses oxytocin neuron responses to IL-1β, and treatment with progesterone or dihydroprogesterone (allopregnanolone precursors) has no effect (Brunton et al., 2012).

Selective actions of the allopregnanolone-opioid inhibitory mechanism that restrains oxytocin and HPA axis responses is indicated by finding that Fos activation in the central amygdala (CeA) by i.v. IL-1β is not different between virgin and late pregnant rats (Brunton et al., 2012). CeA neurons receive direct A2 input (Buller et al., 2001) and also indirect input via the parabrachial nucleus (Buller et al., 2004), and are known to be activated by systemic IL-1β (Ericsson et al., 1994; Xu et al., 1999); while CeA neuron projections to the bed nucleus of stria terminalis (BNST) may regulate oxytocin neurons (Xu et al., 1999). Evidently, because NTS and CeA neurons are activated by i.v. IL-1β in late pregnancy as in virgin rats (Brunton et al., 2005, 2012), it seems that the inhibitory opioid action is not at the level of relays to oxytocin and CRH neurons, but as indicated by measurement of noradrenaline release in the PVN this allostatic mechanism is at the level of these

neurons in the PVN and SON (Brunton et al., 2005).

In conclusion, the allopregnanolone-opioid allostatic mechanism in late pregnancy can be considered as a protective mechanism against preterm activation of oxytocin secretion, e.g. by cytokines signalling infection (Brunton et al., 2014). In support of this consideration is the finding that blocking allopregnanolone production by finasteride treatment in late pregnancy leads to preterm births, and reduced fecundity in rats, with developmental abnormalities in the offspring (Paris et al., 2011b).

5. Perspective

To this point we have developed, and provided evidence for, the concept that there is a combination of allostatic brain changes in normal pregnancy that favour a successful outcome. We have focussed in particular on mechanisms that alter metabolism to favour the needs of the developing fetus, increasing food intake in particular, and on mechanisms that reduce neuroendocrine stress responses. We have considered the molecular mechanisms for increased appetite and reduced stress responses, in terms of changes in the regulatory circuitry in the brain, and pointed out the consequent allostatic load on the pregnant mother that results. We have emphasised the negative consequences of pre-existing obesity, and associated allostatic load, for a successful outcome, and consequent adverse programming effects on offspring.

We do not know yet how pre-existing obesity impacts on the allostatic mechanisms normally regulating appetite circuitry in pregnancy, but suggest this needs investigation. Our studies on stress response mechanisms in pregnancy have shown that repeated social stress programmes the offspring, and their offspring, to be hyper-responsive to stress as reviewed in the next Section. As explained next, allostatic adaptations in the brains of these programmed rats in pregnancy need to be evaluated to seek explanations for trans-generational programming.

6. Prenatal programming of the offspring – next generation maternal brains

6.1. Fetal programming by prenatal stress

During development there are windows where the brain is particularly 'plastic' and thus susceptible to being moulded by external influences. A key time is the prenatal period when exposure to an adverse *in utero* environment, for example as a result of maternal stress, can have long term adverse 'programming' effects on the fetal brain, altering physiology and behaviour and rendering the offspring more vulnerable to certain diseases in later life, shortening lifespan. Moreover, such prenatally stressed (F1) females can, without further prenatal stress, transmit an abnormal phenotype to their offspring (F2), as discussed in Section 6.2.

6.1.1. Fetal programming of the HPA axis

The phenomenon of fetal programming by prenatal stress is well established in rodents, including in rats. The offspring's hypothalamo-pituitary-adrenal (HPA) axis is particularly vulnerable to programming by maternal stress during prenatal development and HPA axis dysregulation in the offspring of stressed dams has been consistently demonstrated with a range of different prenatal stress paradigms (Fride et al., 1986; Weinstock et al., 1992; Henry et al., 1994; Kapoor and Matthews, 2005, 2008; Darnaudery and Maccari, 2008; Emack et al., 2008; Mueller and Bale, 2008). Here the focus is on the offspring of mothers exposed to repeated social stress during late pregnancy (Brunton and Russell, 2010b), a model with which we have the most experience and one which we consider to be ethologically relevant as it reflects the types of stress pregnant women are most likely to encounter, which frequently involve a social component (Valladares et al., 2005, 2009; Lee et al., 2011; Katz, 2012; Laszlo et al., 2013; Mahenge et al., 2013). Other researchers have used a variety of prenatal stress models in rodents, and we refer readers to these studies (Ward, 1972; Fride and Weinstock, 1984; Kinsley and Svare, 1986; Takahashi and Kalin, 1991; Henry et al., 1994; Reul et al., 1994; McCormick et al., 1995; Lordi et al., 1997; Hayashi et al., 1998; Lemaire et al., 2000; Kaiser and Sachser, 2001; Jezova et al., 2002; Smith et al., 2004; Kapoor and Matthews, 2005; Koenig et al., 2005; Tazumi et al., 2005; Lesage et al., 2006; Richardson et al., 2006; Bosch et al., 2007; Mueller and Bale, 2008). In our model, rats are exposed in the last week of pregnancy to a lactating rat (with its litter) for 10 min daily for 5 days (Brunton and Russell, 2010b). Lactating rats are aggressive to intruders, defending their litter, and the intruder females show a submissive response (Neumann et al., 2001), which is accompanied by a robust HPA axis response in virgin rats, but this is attenuated in late pregnancy (Neumann et al., 2001; Brunton and Russell, 2010b).

In adulthood, basal activity of the HPA axis is similar in control and prenatally stressed males (Brunton and Russell, 2010b); however in prenatally stressed females we have reported increased basal secretion of ACTH and corticosterone and elevated levels of *Avp* mRNA in the medial parvocellular PVN (mpPVN) (Brunton and Russell, 2010b). Given that increased *Avp* gene transcription in the mpPVN is an indicator of chronic stress (Ma et al., 1997; Ma and Lightman, 1998), this indicates an increased allostatic load in the prenatally stressed female offspring. Both the female and male offspring of socially stressed dams display stress-induced HPA axis hyperactivity: ACTH and corticosterone secretory responses to both physical (immune challenge with i.v. IL-1β) and psychological (restraint) stressors are greater in amplitude and more prolonged (Brunton and Russell, 2010b), consistent with findings for offspring using other prenatal stress paradigms in rodents (Henry et al., 1994; Kapoor and Matthews, 2005, 2008), but in contrast to studies where the HPA axis was found to be affected only in prenatally stressed female offspring (Weinstock et al., 1992; McCormick et al., 1995). We have also reported enhanced cortisol responses to acute stress in female pigs (males were not studied) born to sows exposed to social stress during pregnancy (Jarvis et al., 2006), further supporting the finding of HPA axis hyperactivity in female prenatally stressed offspring. The greater stress-evoked increase in ACTH and corticosterone secretion in the prenatally stressed female rats than in controls is likely to be a consequence of greater forward drive by the corticotropin releasing hormone (CRH; *Crh*) neurons in the mpPVN, as indicated by greater *Crh* gene expression after stress (Brunton and Russell, 2010b). There is a modest reduction in glucocorticoid receptor (GR; *Nr3c1*) gene expression in the CA2 hippocampal subfield in prenatally stressed females; however the effect on mineralocorticoid receptor (MR; *Nr3c2*) transcription is more marked with considerably lower levels across the different hippocampal subfields, compared with control offspring (Brunton and Russell, 2010b). If translated into reduced receptor abundance, this would be expected to result in less effective glucocorticoid mediated negative feedback control of the HPA axis in prenatally stressed rats (Ratka et al., 1989; Sapolsky et al., 1990), which may explain their prolonged corticosterone responses to acute stress (Brunton and Russell, 2010b).

The mechanisms involved in transmitting the effects of maternal stress exposure during pregnancy to fetuses are not fully understood. Exposure to excessive levels of maternal glucocorticoids (Barbazanges et al., 1996), maternal sympathetic-adrenomedullary hormones (e.g. adrenaline, noradrenaline) (Sandler et al., 1963; Morgan et al., 1972; Sodha et al., 1984), activation of the fetal HPA axis (Ohkawa et al., 1991; Williams et al., 1999; Fujioka et al., 2003) and/or altered maternal behaviour (Leonhardt et al., 2007) may all be contributing factors (for review see (Brunton, 2010)).

6.1.2. Prenatal programming of the oxytocin system

Prenatal restraint stress results in offspring with an anxious and stress hyper-responsive phenotype (Maccari et al., 2014), evidently

involving oxytocin mechanisms in the mother and offspring, and abnormal maternal behaviour in the mother (Gatta et al., 2018). In particular, *Oxt* mRNA is reduced and oxytocin receptor (*Oxtr*) mRNA expression is increased in the hippocampus (the cellular origin of *Oxt* mRNA in the hippocampus is not clear) (Gatta et al., 2018). An earlier study reported that stress exposure during pregnancy reduces postpartum maternal care, specifically in dams previously characterised as showing high levels of licking and grooming behaviour (Champagne and Meaney, 2006). Importantly, the female offspring of these mothers display a similar deficit in maternal care when they become mothers. In both instances (i.e. the stressed mother and her adult offspring) this behaviour was associated with reduced oxytocin receptor binding in the BNST, medial preoptic area (MPOA) and CeA during lactation compared with non-stressed controls (Champagne and Meaney, 2006).

6.1.3. Neuroactive steroids and HPA axis responses to stress

Neuroactive steroids are a class of steroids that are synthesised in the brain, either *de novo* or from precursors entering the brain from the periphery (often referred to as neurosteroids; see Section 4.6), or are produced by a peripheral endocrine gland and then enter the brain to influence function. Rather than acting via classical steroid receptors, neuroactive steroids typically modulate the excitability of neurons via rapid non-genomic actions through interactions with ligand-gated ion channels. Allopregnanolone, (the neuroactive steroid metabolite of progesterone) has been studied extensively and is of particular relevance here because of its anxiolytic and stress-reducing effects (Patchev et al., 1994, 1996; Bitran et al., 1995; Brunton et al., 2009). As mentioned above (Section 4.6), allopregnanolone exerts inhibitory actions on neurotransmission by acting as a positive allosteric modulator of the $GABA_A$ receptor (Lambert et al., 1990; Morrow et al., 1990; Paul and Purdy, 1992). Hence, in rodents, allopregnanolone has been shown to suppress stress-induced activity of the HPA axis, inhibit stimulated CRH release from hypothalamic explants and inhibit spontaneous firing of presumptive CRH neurons in the mpPVN (Patchev et al., 1994, 1996; Brunton et al., 2009; Gunn et al., 2013). In contrast, blocking allopregnanolone synthesis with the 5α-reductase inhibitor, finasteride, prolongs the ACTH response to stress (Brunton et al., 2009). Furthermore, in humans, several mood and stress-related disorders have been linked to lower levels of allopregnanolone in the circulation and cerebrospinal fluid (Rasmusson et al., 2006; Hellgren et al., 2014; Schule et al., 2014). In light of this evidence, we and others have investigated a potential link between deficiencies in neurosteroid production and enduring effects of prenatal stress on the adult offspring.

6.1.4. Prenatal stress and neuroactive steroids in offspring

Maternal exposure to repeated social stress in pregnancy results in significantly lower gene expression for 5α-reductase in the brainstem of the adult female offspring, and also in the hypothalamus and the liver of male offspring (Brunton et al., 2013, 2015). Similarly, other models of prenatal stress or prenatal glucocorticoid exposure have reported reduced 5α-reductase activity and gene transcription in the brains of fetuses and juveniles, as well as lower circulating and brain concentrations of allopregnanolone (Ordyan and Pivina, 2005; McKendry et al., 2010; Paris et al., 2011a; Paris and Frye, 2011a, 2011b; Yawno et al., 2014). Together these data indicate that prenatal stress exposure programs reduced capacity for neurosteroid production in the offspring. Accordingly, we have found that both allopregnanolone replacement and adenovirus-mediated up-regulation of *Srd5a* and *Akr1c4* mRNA expression in the NTS normalises HPA axis responses to acute stress in adult prenatally stressed female rats (Brunton et al., 2015).

The mechanisms through which allopregnanolone suppresses hyperactive HPA axis responses to stress in prenatally stressed offspring have not been elucidated, however as described in Section 4.6.2, we previously demonstrated that in pregnancy, allopregnanolone up-regulates an inhibitory opioid mechanism that restrains HPA axis responses to stress and this mechanism can be induced in non-pregnant females with exogenous allopregnanolone (Brunton et al., 2009). It is not clear if the same mechanism is at play in prenatally stressed rats administered allopregnanolone. Given we did not detect any change in *Srd5a* mRNA in the PVN of prenatally stressed female rats (Brunton et al., 2015), local allopregnanolone concentrations in the PVN and direct actions on $GABA_A$ receptors controlling CRH neurons is not expected to be reduced (Gunn et al., 2013).

6.1.5. Fetal programming of anxiety-like behaviour

In addition to HPA axis hyperactivity, prenatal stress is frequently linked with heightened anxiety-like behaviour in the offspring in rodents (Fride and Weinstock, 1988; Vallee et al., 1997; Zuena et al., 2008; Fan et al., 2009) and pigs (Rutherford et al., 2014). Maternal exposure to social stress during pregnancy results in an anxious phenotype in the adult male offspring, however at least in the case of rodents, the female offspring are seemingly spared (Brunton and Russell, 2010b; Brunton et al., 2011). Control and prenatally stressed females display similar anxiety-like behaviours, despite clear changes across the estrous cycle. Regardless of prenatal experience, the lowest levels of anxiety-related behaviour are observed at proestrus/estrus (Brunton and Russell, 2010b), probably as a result of estradiol actions (Walf and Frye, 2007).

6.1.6. Fetal programming of offspring social memory

The ability to form and recall social memories is vital for developing and maintaining social relationships, such as pair bonds, parent-infant bonds and social hierarchies (Ferguson et al., 2002; Insel and Fernald, 2004). Despite similar preferences for social interactions, female, but not male, offspring of dams exposed to social stress during pregnancy display impaired social memory compared with control rats (Grundwald et al., 2016). An impairment of social memory has also been reported in male offspring (females were not studied) using a different prenatal stress model (de Souza et al., 2013); hence vulnerability to fetal programming of social memory in the offspring may be sex-specific depending on the nature of the prenatal stress experienced.

This deficit in social recognition appears to be specific for social odours and is not a result of impaired olfaction as prenatally stressed females form olfactory memories for non-social odours just like control females do (Grundwald et al., 2016). Social recognition differs from spatial memory or object recognition processing and as such is regulated by distinct neural circuits and mechanisms. Of critical importance for social memory are the central actions of AVP, primarily via AVP-1a receptors (*Avpr1a*) in the lateral septum (Engelmann and Landgraf, 1994; Landgraf et al., 1995, 2003). Hence, centrally administered AVP or *Avpr1a* over-expression in the septum enhances social memory (Le Moal et al., 1987; Engelmann and Landgraf, 1994; Engelmann et al., 1994; Landgraf et al., 2003), whereas social memory is impaired by central administration of an Avpr1a antagonist or antisense oligonucleotides against *Avpr1a*, and is also impaired in AVP deficient rats or in *Avpr1a* knock-out mice (Engelmann and Landgraf, 1994; Landgraf et al., 1995; Everts and Koolhaas, 1999; Bielsky et al., 2004). In accordance, the social memory deficit displayed in prenatally stressed female rats is associated with reduced *Avpr1a* gene expression in the lateral septum and in the BNST (Grundwald et al., 2016), which sends vasopressinergic projections to the lateral septum (Caffe et al., 1987; de Vries and Miller, 1998). It is unclear whether this leads to altered AVP signalling; however, reduced Avpr1a activation in the lateral septum evidently contributes to social memory deficits in rats exposed to stress in early post-natal life (Lukas et al., 2011). Interestingly, polymorphisms in the human *AVPR1A* gene have been associated with an increased risk of autism (Tansey et al., 2011), poorer performance in facial affect recognition tests in schizophrenic patients (Golimbet et al., 2015) and a greater negative impact of childhood adversity on social integration (Liu et al., 2015), further supporting a role for altered Avpr1a expression in altered social behaviour.

The central oxytocin system also plays a role in social memory

processing (Engelmann et al., 1998; Ferguson et al., 2000, 2001; Choleris et al., 2003; Lee et al., 2008); however, we found no differences in *Oxtr* mRNA expression between control and prenatally stressed offspring in the lateral septum, BNST, MPOA or medial amygdala (Grundwald et al., 2016). Even so, we cannot rule out altered oxytocin signalling in social memory deficits in prenatally stressed rats, as changes in oxytocin synthesis or release within the brain would also be expected to contribute, as has been previously reported (Lukas et al., 2013), including in the case of prenatally stressed offspring (Lee et al., 2007; de Souza et al., 2013).

6.1.7. *Fetal programming of metabolic processes*

In addition to changes in the brain and behaviour, prenatally stressed offspring also exhibit a metabolic phenotype, though the female offspring often seem to be more sensitive (Brunton et al., 2013; Dearden et al., 2018). Using our maternal social stress model, female offspring typically have lower birth weights than control offspring (Brunton and Russell, 2010b; Brunton et al., 2013); however, catch-up growth occurs rapidly in the post-natal period (Brunton et al., 2013). In early adulthood (age 3 months), prenatally stressed females display normal insulin responses to glucose loading, however by 6 months of age these rats are hyper-insulinaemic following an oral glucose load, indicating these rats have to secrete more insulin in order to restore glucose homeostasis, and that maternal prenatal stress exposure increases the propensity for developing insulin resistance in the adult offspring (Brunton et al., 2013).

Concomitant with these changes in glucose regulation are changes in the expression of genes known to be important in regulating lipid metabolism in the liver, muscle and adipose tissue (Fig. 4). For example, *Pgc1α* (*Ppargc1a*) expression in the liver is around 40% lower in prenatally stressed females compared with controls (Brunton et al., 2013) and a similar finding has been reported in the offspring of rats exposed to the synthetic glucocorticoid, dexamethasone during pregnancy (Drake et al., 2010). This is important, as Pgc1α plays a key role in regulating lipid homeostasis and hepatic Pgc1α deficiency is associated with hepatic steatosis in animals and non-alcoholic fatty liver disease in humans (Akiyama et al., 2001; Leone et al., 2005; Westerbacka et al., 2007; Estall et al., 2009), indicating that prenatally stressed rats may be more prone to fat accumulation in the liver. Although no differences were found in hepatic triglyceride concentrations in the liver of these rats, circulating triglycerides were elevated in the prenatally stressed male offspring fed a standard rat diet (Brunton et al., 2013).

Although these rats were not obese, we would predict that with increased allostatic load e.g. through advancing age and/or access to a high fat diet and/or chronic stress exposure these prenatally stressed rats may be more likely to develop a fatty liver, consistent with reports from rats exposed to dexamethasone during prenatal life (Drake et al., 2010). Expression of mRNA for peroxisome proliferator-activated receptor-α (*Pparα*) is also reduced in skeletal muscle of female prenatally stressed rats, further supporting the conclusion that prenatal stress impacts lipid utilisation, which may also contribute to lipid accumulation and insulin resistance (Kim et al., 2000; Muoio et al., 2002).

In subcutaneous adipose tissue, there is marked down-regulation in gene expression for enzymes involved in lipid metabolism in female prenatally stressed rats, including adipose triglyceride lipase (*Atgl; Pnpla2*), diacylglycerol acyltransferase 2 (*Dgat2*) and phosphoenolpyruvate carboxykinase (*Pepck; Pck1*) (Brunton et al., 2013), indicating reduced lipid turnover in female prenatally stressed rats. Atgl is important for fat cell lipolysis to mobilise free fatty acids from adipose stores. Indeed, *Atgl* knockout mice have enlarged fat depots and are not able to effectively liberate sufficient fatty acids to maintain energy homeostasis (Schoiswohl et al., 2010). The mechanisms involved are unclear; however Atgl expression in adipose is up-regulated by glucocorticoids (Serr et al., 2011) and down-regulated by insulin resistance and obesity (Yao-Borengasser et al., 2011).

Consistent with this, was the finding of reduced 11β-hydroxysteroid dehydrogenase type 1 (*Hsd11b1*) mRNA expression in the adipose tissue of prenatally stressed females (Brunton et al., 2013), which is indicative of reduced glucocorticoid re-generation. Intriguingly, leptin gene

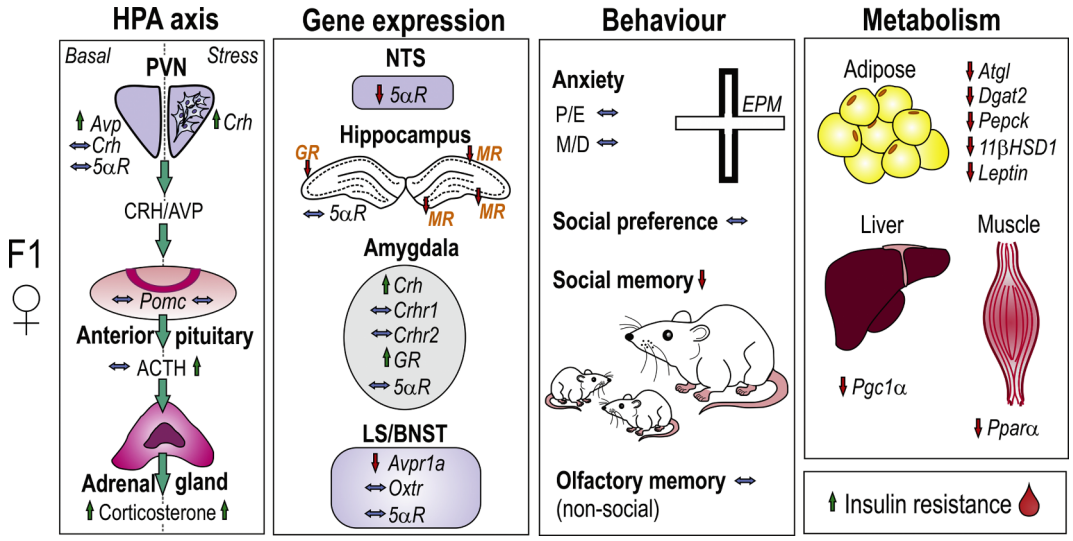

Fig. 4. Summary of the programmed phenotypes in F1 female prenatally stressed rats. Compared with non-stressed control offspring, rats born to dams exposed to social stress during pregnancy display HPA axis dysfunction (greater basal and stress-induced activity), altered behaviour (impaired social memory) and abnormal metabolism (impaired lipid metabolism, abnormal glucose regulation, insulin resistance). These phenotypes are associated with differential gene expression in the brain and the periphery. Green upward arrow indicates greater expression, red downward arrow indicates lower expression and blue double-ended horizontal arrow indicates no change relative to controls. Abbreviations: 5αR, 5α-reductase; 11β-HSD1, 11β-hydroxysteroid dehydrogenase-1; Atgl, adipose triglyceride lipase; Avp, arginine vasopressin; BNST, bed nucleus of the stria terminalis; Crh, corticotropin releasing hormone; Crhr1, CRH receptor 1; Crh2, CRH receptor 2; Dgat2, diacylglycerol acyltransferase 2; EPM, elevated plus maze; GR, glucocorticoid receptor; LS, lateral septum; M/D, metestrus/diestrus; MR, mineralocorticoid receptor; NTS, nucleus tractus solitarii; Oxtr, oxytocin receptor; P/E, proestrus/estrus; PEPCK, phosphoenolpyruvate carboxykinase; Pgc1α, peroxisome proliferator-activated receptor gamma, coactivator-1α; Pparα, peroxisome proliferator activated receptor-α; PVN, paraventricular nucleus. Based on data from: (Brunton and Russell, 2010b; Brunton et al., 2011, 2013, 2015; Grundwald and Brunton, 2015; Grundwald et al., 2016). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

expression in the subcutaneous adipose tissue of prenatally stressed females is around 60% lower than that observed in control females (with a similar trend reported in prenatally stressed males) (Brunton et al., 2013). This indicates that leptin signalling to the hypothalamic neurons regulating appetite and energy balance may be impaired as a result of prenatal stress. In this study the rats were not obese, however given leptin deficiency leads to obesity (Schwartz et al., 1996); any reduction in leptin production by adipocytes could predispose prenatally stressed rats to obesity if access to a high fat diet were provided. In support, visceral adiposity induced by an obesogenic diet is increased to a greater extent in the female (but not in the male) offspring of dams exposed to stress during pregnancy compared with those born to unstressed dams (Paternain et al., 2013). Thus prenatal stress is associated with sex-specific changes in the control of glucose homeostasis and in the expression of genes involved in lipid metabolism which may increase the risk of metabolic dysfunction. Further studies are needed to fully understand the potential impact of these changes on long term health.

The programmed phenotypes described in F1 prenatally stressed female rats (e.g. HPA axis dysfunction; altered metabolic function) can be considered to increase allostatic load in these rats (Fig. 4), which may lead to an additional burden when these animals themselves become pregnant and could contribute to trans-generational programming. This has still to be directly investigated. However, in support of this proposal, exposure to prenatal stress has been demonstrated to prevent the down-regulation of HPA axis activity typically observed during lactation in F1 offspring (Bosch et al., 2007), indicating that at least one of the allostatic mechanisms that emerges in pregnancy (and is maintained throughout lactation, i.e. HPA axis hyporesponsiveness) is disrupted by prenatal stress exposure.

6.2. Transgenerational programming

As described above, a plethora of evidence supports the concept of fetal programming of the brain and behaviour by prenatal stress, however as yet the underlying mechanisms are not completely understood; though stable changes in gene function are evident and likely to play a role in shaping programmed phenotypes. As a result, much focus has centred on epigenetic modifications, as a means to 'code' non-genomic alterations in gene expression (Maccari et al., 2014; Bale, 2015). Such changes may be long-lasting and if the germ cells are also affected opens up the possibility of transgenerational effects of prenatal stress exposure (Bale, 2015); hence recent studies on the impact of prenatal stress on the offspring have been extended to include subsequent generations, without further imposed stress during pregnancy. As discussed above, the adult offspring (F1 generation) of mothers exposed to social stress during pregnancy clearly display an abnormal metabolic, neuroendocrine and behavioural phenotype, with altered gene expression in the brain (Brunton and Russell, 2010b; Brunton et al., 2011, 2013; Grundwald et al., 2016).

While it is not known whether normal allostatic adaptations in the maternal brain in these rats occur in pregnancy, from this base, we have tested whether prenatally stressed F1 females can transmit an abnormal phenotype to their F2 offspring, without further imposed stress.

6.2.1. HPA axis function in second generation (F2) prenatally stressed females

In particular, we have investigated whether the effects of social stress exposure during pregnancy on offspring phenotype are transmitted to the second (F2) generation via the maternal line. To do this prenatally stressed females (F1 generation) born to dams exposed to social stress during the last week of pregnancy (5 × 10 min exposures to a lactating female, as before (Brunton and Russell, 2010b)) were mated with naïve non-stressed males. Next, in the absence of any interventions in the F1 female's pregnancy, we investigated the impact on HPA axis function and stress-related behaviours in the adult F2 offspring ('granddaughters'). Importantly, we found that the F1 females supported an evidently normal pregnancy, with regard to length of gestation, litter size, birth weight and sex ratio (Grundwald and Brunton, 2015). Moreover, the maternal behaviour of the F1 females does not appear to be abnormal, as assessed by several components of maternal behaviour; e.g. nursing, licking and grooming, pup retrieval (Grundwald and Brunton, unpublished observations).

Compared with controls, adult female F2 prenatally stressed rats display greater activation of the HPA axis in response to a physical stressor (immune challenge with acute i.v. IL-1β injection) and a prolonged ACTH response following exposure to a psychological stressor (30 min restraint) (Grundwald and Brunton, 2015). Consistent with the F1 generation phenotype, the greater ACTH and corticosterone secretory response to stress in the F2 females may be explained by increased hypothalamic drive to the anterior pituitary, as post-acute stress *Crh* and *Avp* gene transcription in the mpPVN is more strongly increased in the F2 prenatally stressed females than in F2 controls; while reduced hippocampal GR and MR gene expression may be indicative of less efficient glucocorticoid negative feedback inhibition and contribute to prolonged HPA axis stress responses (Grundwald and Brunton, 2015). Whether forward excitatory drive to the mpPVN neurons (e.g. by noradrenergic inputs) is enhanced or whether there are deficits in neurosteroid signalling mechanisms in the F2 prenatally stressed offspring remains to be elucidated.

6.2.2. Anxiety-related behaviour in second generation (F2) prenatally stressed females

Despite finding no difference in anxiety-like behaviour between female control and prenatally stressed F1 offspring (Brunton and Russell, 2010b), there is evidence for alterations in anxious behaviour in the prenatally stressed granddaughters (F2). During diestrus/metestrus, anxiety-like behaviour in the light-dark box and on the elevated plus maze is similar between F2 prenatally stressed females and F2 controls (Grundwald and Brunton, 2015), consistent with findings in the F1 females described in Section 6.1.5 (Brunton and Russell, 2010b). However, while F2 control females display a marked reduction in anxiety-like behaviour at proestrus-estrus (Grundwald and Brunton, 2015), consistent with other studies and our F1 control females (Frye et al., 2000; Marcondes et al., 2001; Brunton and Russell, 2010b), the prenatally stressed F2 females do not show this presumably estrogen-related reduction in anxious behaviour (Grundwald and Brunton, 2015). Estradiol is known to reduce anxiety-like behaviour in female rats (Marcondes et al., 2001); hence, sensitivity to estradiol may be reduced in F2 prenatally stressed females, but this needs further study. Circulating and central levels of allopregnanolone are also greater at proestrus, when females are less anxious (Frye et al., 2000) and blocking allopregnanolone synthesis with finasteride increases anxiety-like behaviour (Frye and Walf, 2002). Hence, if central 5α-reductase activity is reduced (and by extension, allopregnanolone production) in the prenatally stressed F2 females, as reported in the F1 offspring (Brunton et al., 2015), this would be expected to contribute to altered anxiety-like behaviour; again this issue needs further investigation.

6.2.3. Mechanisms of fetal programming of gene function by prenatal stress

Studies examining HPA axis and behavioural phenotypes in the F3 offspring could shed light on whether the transgenerational impacts of maternal stress are mediated through changes in the somatic cells and/or the primordial germ cells of the F1 fetuses (Bale, 2015). The mechanisms through which stress exposure during pregnancy exerts long-term effects on gene expression in the brains of the offspring, and indeed in subsequent generations are unclear, however epigenetic mechanisms probably play a role.

There are several means through which gene transcription can be modified, such as DNA methylation, hydroxymethylation and histone modifications (e.g. acetylation) (Wade et al., 1997; Jenuwein, 2001; Shiio and Eisenman, 2003; Shilatifard, 2006; Kriaucionis and Heintz,

2009). Evidently the most commonly studied process with respect to early life stress is alterations in DNA methylation. When DNA methylation occurs in the regulatory regions of genes, it is well established to silence gene expression by directly interfering with the binding of transcription factors to their response element (Comb and Goodman, 1990). Indeed, reduced methylation of the *Crh* promoter and increased methylation of the GR (*Nr3c1*) promoter have been reported in the hypothalamus from mice exposed to prenatal stress in early pregnancy that show hyperactive HPA axis stress responses associated with higher levels of *Crh* and lower expression of *Nr3c1* mRNA in the brain (Mueller and Bale, 2008). Although data from human brains are limited, DNA hypermethylation of the *NR3C1* promoter is associated with reduced *NR3C1* mRNA expression in the hippocampus of adults who experienced abuse in childhood (McGowan et al., 2009), further supporting a role for stress-induced epigenetic changes and indicating there may be a common mechanism that mediates the impact of an adverse environment experienced prenatally or in childhood on subsequent gene expression and function.

As well as the processes outlined above, small non-coding microRNAs (miR) can induce gene silencing by binding to target mRNA and inducing degradation or translation repression (Bartel, 2004; Flanagan and Wild, 2007). Indeed, in mice, paternal chronic stress exposure before conception, leads to offspring with altered HPA axis function and this is associated with changes in specific miRs in the father's sperm (Rodgers et al., 2013, 2015). Hence research focussing on the role of miRs in fetal programming by maternal stress is expected to improve our understanding over the coming years. It remains to be determined whether altered miR expression or increased methylation underlies reduced 5α-reductase gene expression in prenatally stressed rats.

7. Future perspectives

An alternative mechanism for trans-generational programming is that the altered brain phenotype of the F1 prenatally stressed females alters the 'normal' allostatic adjustments to pregnancy, resulting in adverse programming from signals arising in the pregnancy and transmitted to the developing foetuses (Fig. 5). Hence, this possibility does not involve transmission by gametes, and as a general hypothesis this can be tested by intervening and resetting altered central mechanisms, to normalise the F1 prenatal stress phenotype. This might involve focus on a single gene product (e.g. 5α-reductase) or several genes.

Our concept here is that allostatic changes in normal pregnancy in combination with allostatic load from adverse prenatal programming/pre-pregnancy obesity and/or chronic stress is risky for the mother and offspring and will give a bad start to life (Fig. 5), and that this can be assessed in rodent models. As allostasis by definition involves integrated responses organised by the brain, specifically, we propose addressing maternal brain changes in pregnancy with additional allostatic load of programming of the pre-maternal brain by prenatal stress.

Certainly, at present information is lacking about whether maternal brain changes in pregnancy in either F1 or F2 prenatally stressed females are as they are in normal rats, or whether there are differences in expression of genes concerned with allostasis in pregnancy, for instance those genes that govern neuroendocrine stress responses. We also do not know how obesity in pregnancy interacts with changes in the brain in pregnancy, either alone or in combination with stress, and in particular in pregnancies in F1 prenatally stressed females. We suggest that such studies will closely represent current challenges to many women in pregnancy.

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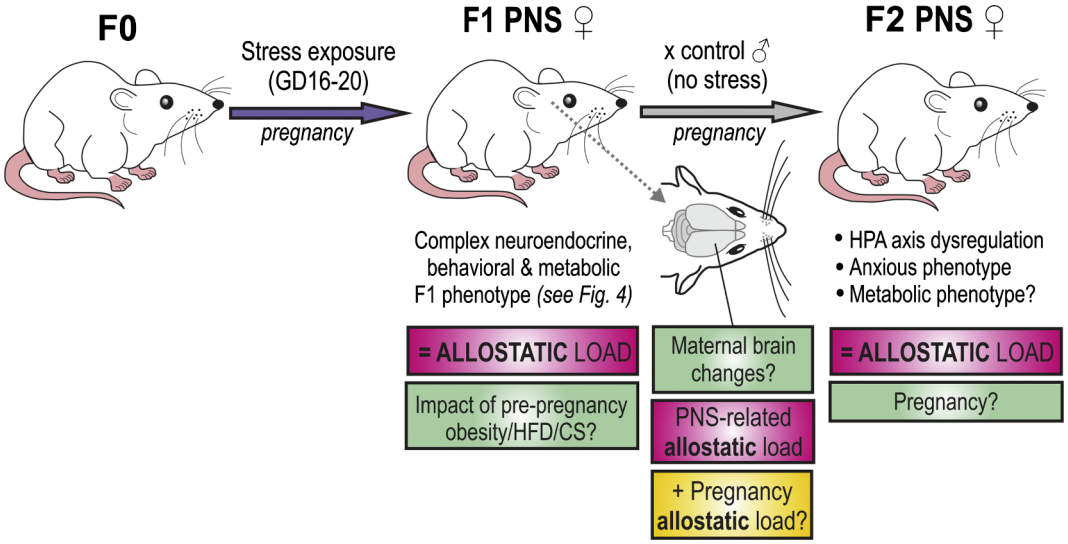

Fig. 5. Allostasis and transgenerational programming. Repeated social stress on gestational days (GD) 16–20 in F0 dams produces prenatally stressed (PNS) F1 female offspring with complex neuroendocrine, behavioural and metabolic phenotypes (detailed in Fig. 4) which are expected to increase allostatic load. F1 female offspring can support pregnancy and rear F2 offspring, however it is unclear whether the maternal brain adaptations in the F1 PNS females occur as they do in a normal pregnancy. We propose that the increased allostatic load resulting from prenatal stress exposure, interacts with normal allostatic load in pregnancy to underlie adverse programming of the F2 offspring, e.g. of the hypothalamo-pituitary-adrenal (HPA) axis. Moreover, the altered brain phenotype of the F1 PNS females may lead to alterations in the pregnancy-related allostatic adjustments to pregnancy. Additional allostatic load during pregnancy as a result of e.g. pre-pregnancy obesity and/or high fat diet (HFD) and/or chronic stress (CS) may also produce a programmed phenotype in the offspring, though this has yet to be tested in this model. It remains to be established whether F2 offspring can maintain a pregnancy and rear offspring. However, we propose studies focussing on the maternal brains of pregnant F1 and F2 females are needed to better understand the impact of increased allostatic load on trans-generational programming.

Declaration of conflict of interest

The authors have nothing to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2019.02.003.

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