REVIEW

Hormonal and nutritional regulation of postnatal hypothalamic development

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Abstract

The hypothalamus is a key centre for regulation of vital physiological functions, such as appetite, stress responsiveness and reproduction. Development of the different hypothalamic nuclei and its major neuronal populations begins prenatally in both altricial and precocial species, with the fine tuning of neuronal connectivity and attainment of adult function established postnatally and maintained throughout adult life. The perinatal period is highly susceptible to environmental insults that, by disrupting critical developmental processes, can set the tone for the establishment of adult functionality. Here, we review the most recent knowledge regarding the major postnatal milestones in the development of metabolic, stress and reproductive hypothalamic circuitries, in the rodent, with a particular focus on perinatal programming of these circuitries by hormonal and nutritional influences. We also review the evidence for the continuous development of the hypothalamus in the adult brain, through changes in neurogenesis, synaptogenesis and epigenetic modifications. This degree of plasticity has encouraging implications for the ability of the hypothalamus to at least partially reverse the effects of perinatal mal-programming.

Key Words

- ▶ metabolism
- ▶ stress
- ▶ fertility
- ▶ perinatal
- ▶ programming

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The architecture of the hypothalamus

Neuroanatomically, the adult hypothalamus in humans and rodent models can be sub-divided into anterior, tuberal and posterior, with further subdivisions of each of these depending upon rostrocaudal location and neuronal subtypes present (Pearson & Placzek 2013, Watts 2015). The various neuronal populations found throughout the hypothalamus are drivers of key biological processes in the mature animal, including feeding and metabolism, stress responsiveness, reproduction, thermoregulation, sleep circadian rhythms and others (Fig. 1). For example, the neuropeptide Y (NPY)/agouti-related protein (AgRP)- and pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART)- containing neurons of the arcuate nucleus (ARC) respond to circulating

satiety hormones, including ghrelin, leptin and insulin to drive (NPY/AgRP; ghrelin) and suppress (POMC/CART; leptin, insulin) feeding (Andermann & Lowell 2017). The corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) neurons of the paraventricular nucleus (PVN) respond to stressful stimuli to stimulate release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, which subsequently drives the release of corticosterone from the adrenal cortex (Herman *et al.* 2016). The gonadotropin-releasing hormone (GnRH) neurons of the preoptic area (POA) respond to kisspeptin (Irwig *et al.* 2004, Han *et al.* 2005, Messenger *et al.* 2005) and other neuropeptides, such as RFamide-related peptides (Ukena *et al.* 2002, Ubuka *et al.* 2009), to regulate

Figure 1

The hypothalamus is a driver of key biological processes in the mature animal, including feeding and metabolism, stress responsiveness and reproductive function. AgRP, agouti-related protein; ARC, arcuate nucleus of the hypothalamus; AVP, arginine vasopressin; CART, cocaine and amphetamine-related transcript; CRH, corticotropin-releasing hormone; DMH, dorsomedial hypothalamus; GnRH, gonadotropin-releasing hormone; LH, lateral hypothalamus; ME, median eminence; NPY, neuropeptide Y; OT, oxytocin; POA, preoptic area; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus of the hypothalamus; SCN, suprachiasmatic nucleus; VMH, ventromedial nucleus of the hypothalamus; 3V, third ventricle.

the pulsatile and tonic release of luteinizing hormone and follicle-stimulating hormone (FSH), which, in females, stimulate ovulation and support ovarian follicle maturation (Krsmanovic *et al.* 2009, Ohkura *et al.* 2009). Connections throughout the hypothalamus integrate these functions. For example, NPY/AgRP neurons project to the PVN to convey feeding information to extra-hypothalamic brain regions, and this transmission can be curtailed by CRH neurons (Cowley *et al.* 1999, Lu *et al.* 2003), facilitating the modulation of food intake by stress. Likewise, kisspeptin fibres originating from the ARC and anteroventral periventricular nucleus (AVPV) can also be found in the PVN and limbic structures (Yeo & Herbison 2011, Yip *et al.* 2015) and facilitate modulation of the reproductive axis by stress (Herman *et al.* 2005).

Establishing the appropriate hypothalamic connectivity is thus essential for an individual's survival, wellbeing and reproduction. It is noteworthy, then, that these circuits are highly vulnerable to early life environmental influences, including by nutritional and hormonal factors, particularly at specific phases of an individual's development (Spencer 2013). However, there are data to suggest that the establishment of this circuitry

also displays remarkable resilience in the face of many environmental challenges (e.g. Parker *et al.* 2005, Macri *et al.* 2007, Bellisario *et al.* 2014, Sominsky *et al.* 2017a,b). In this review, we will discuss the role of hormonal and nutritional regulators of prenatal and postnatal hypothalamic development whose actions shape and define later-life hypothalamic function (Fig. 2).

Prenatal hypothalamic development

The hypothalamus develops from the rostral/ventral diencephalon from about mid-gestation (gestational day 8.5) in the rodent (Shimamura *et al.* 1995). The patterning of the neural tube into the developing hypothalamus, as well as early patterning within the hypothalamus has been covered in detail in recent excellent reviews (Bedont *et al.* 2015, Burbidge *et al.* 2016, Xie & Dorsky 2017). Briefly, following early patterning under the influence of *Shh*, BMPs (dorsoventral) and Wnts (anteroposterior), the hypothalamus can be subdivided into the major regions listed earlier. Each region in turn is then divided into specific nuclei, in a process of

Figure 2

Major milestones of postnatal hypothalamic development in rodents. At birth, hypothalamic neuronal circuitry is a rudimentary scaffold of pioneering axonal projections that are used as guides upon which postnatal projections form and elaborate. A postnatal leptin surge drives the development of neuronal projections from the arcuate nucleus of the hypothalamus (ARC) to dorsomedial hypothalamus (DMH) at postnatal day 6 (P6), to paraventricular nucleus of the hypothalamus (PVN) at P8-10, and to lateral hypothalamus (LH) at P12. A subsequent rise in the levels of ghrelin curbs excessive development of these neuronal connections. The first two weeks of rodent postnatal life are known as a stress hypo-responsive period, associated with low levels of circulating glucocorticoids, increased gene expression of corticotropin-releasing hormone (CRH) and decreased expression of the glucocorticoid receptor (GR). Hypothalamic reproductive circuitry rapidly develops during the first three weeks of life, with continuous increase in the expression of kisspeptin neurons in the anteroventral periventricular nucleus (AVPV) and the ARC, triggering the establishment of GnRH pulsatility. Puberty onset is further triggered by leptin that acts as an indirect permissive signal, particularly in females. Leptin levels increase after weaning, corresponding with the increasing body mass. The development of the hypothalamus does not stop at puberty, but is maintained to some degree throughout life, with continuous changes in neurogenesis, synaptic remodelling and epigenetic modifications. Note, hormonal profiles are indicative only and are not drawn to scale.

ever-finer boundary-forming morphogen gradients that define hypothalamic subdomains or nuclei (Burbridge *et al.* 2016). Hypothalamic nuclei have been described as being organised in a 'patchwork' (Bedont *et al.* 2015), mainly because they lack the tidy and obvious lamination exhibited by the neocortex. The molecular origins and functional significance of organisation within the hypothalamus is only just beginning to be understood and will come into clearer focus as hypothalamic lineage relationships are slowly teased apart.

Following initial patterning, subsequent patterns of gene expression act to define the terminally differentiated phenotype of hypothalamic neurons (Campbell *et al.* 2017). In temporal order of expression, these include genes

that regulate cell type-specific migration (for cells that actively migrate) (see for example: Cariboni *et al.* 2015, Di Sante *et al.* 2015, Giacobini 2015, Howard *et al.* 2016, Hutchins *et al.* 2016), and axonal and dendritic growth and guidance (see for example: Low *et al.* 2012, Liao *et al.* 2015, Sanders *et al.* 2017). Cell type-specific expression of neurotransmitter/peptides is also a critical developmental step, but this appears to occur at different times across development for different neurons (e.g. GnRH neurons express GnRH prior to and during migration, whereas orexin neurons of the lateral hypothalamus (LH) do not appear to express orexin until situated laterally in the LH (Twigg 2017, personal observation). As a consequence of this prenatal developmental sequence, by the time of

birth in the rodent most hypothalamic neurons are in their adult locations, and express the neurotransmitter(s)/peptide(s) that will define them, and their functions throughout life. In addition, they have extended axons to key target areas and have developed dendrites to synapse with incoming axons. This developmental sequence gives rise to a rudimentary neural circuitry poised to be further elaborated and synaptically sculpted by important environmental factors encountered by the freely living individual after birth. Although we will not cover details of development nor prenatal developmental programming in this review, there is some evidence that metabolic and hormonal perturbation of prenatal development occurs in some of these systems (Chang *et al.* 2008, Sanders *et al.* 2014, Moore & Campbell 2017).

Neonatal hypothalamic development

Metabolic circuitry

Despite this prenatal development of hypothalamic neurons, by the time of birth in rodents the pattern and function of axonal connections throughout the hypothalamus is still immature, particularly in the ARC. The LH melanin-concentrating hormone neurons develop in the embryonic phase (Croizier *et al.* 2011) and projections between the dorsomedial hypothalamic nucleus (DMH) and the PVN and LH are present and functional before postnatal day 6 (P6) (Bouret *et al.* 2004a). Projections from the VMH to the forebrain are in place by birth (Cheung *et al.* 2013). However, axonal projections from the ARC to the DMH are not visible with neuronal tract tracing with DiI until P6 in the mouse. Similarly, ARC to PVN connections are not seen before P8–10, and ARC to LH connections appear at around P12 (Bouret *et al.* 2004a). As such, DMH neurons are responsive to leptin at P6 but PVN neurons are not (Bouret *et al.* 2004a).

How such development is restricted to such specific time periods is not clear. Neurodevelopmental genes including *Shh*, a morphogen that regulates neuronal development, are differentially methylated in the ARC compared with PVN, co-incident with the timing of this development (Li *et al.* 2014), which suggests epigenetic mechanisms are likely to contribute. Receptors for some neurotrophic hormones may also be transiently expressed in developing ARC neurons (Betley *et al.* 2013). Specific developmental signals also differentially trigger development of different neuronal subtypes. For instance, leptin stimulation of a STAT3-dependent pathway is

needed for ARC POMC neuron development, but not for AgRP projections (Bouret *et al.* 2012).

Once axonal connections are established, synapse formation and maturation takes place. Early electron microscopy studies showed a paucity of synapses in the ARC at birth, with the number increasing from P5 to adulthood (Matsumoto & Arai 1976). These synapses continue to mature functionally from birth through to adulthood with, for instance, PVN neurons being relatively unresponsive to melanocortin at one week of age but highly responsive in the juvenile phase (Melnick *et al.* 2007). It is noteworthy that inputs to NPY/AgRP/GABA neurons in the ARC are predominantly excitatory during the first three weeks of life in the mouse. The switch to inhibitory inputs within this circuitry comes as a result of KATP channel expression and does not occur until around P21 (Juan De Solis *et al.* 2016).

In 1998, Ahima and colleagues identified a profile of changes in circulating leptin in the neonatal mouse consistent with this hormone performing a neurotrophic function, since at this time neonatal mice are relatively impervious to the anorexigenic effects of leptin (Ahima *et al.* 1998, Mistry *et al.* 1999). Thus, leptin levels remain low in neonatal mice and rats until after P4 at which time they sharply increase over the course of 10–12 days before falling to adult levels (Ahima *et al.* 1998, Ahima & Hileman 2000, Delahaye *et al.* 2008, Cottrell *et al.* 2009). Bouret and Simerly later expanded on this work to show this leptin surge is responsible for stimulating the development of connections between the ARC and LH (P12), DMH (P6) and PVN (P8–10) in the mouse (Bouret *et al.* 2004a,b, Bouret & Simerly 2006). There is further evidence from the Bouret group that ghrelin may similarly act as a trophic signal in the neonatal phase, in this case, with circulating ghrelin concentrations increasing between P10 and P14 and at this point acting to curtail leptin-stimulated neurite growth (Steculorum *et al.* 2015). Insulin is a third hormone important in the development of this circuitry. Although insulin remains relatively constant in early postnatal life, with a gradual increase to adult levels just prior to puberty (Ahima *et al.* 1998), perturbations in insulin signalling can also influence the development of hypothalamic metabolic circuitry (Plagemann *et al.* 1992, 1999, Vogt *et al.* 2014).

Perinatal programming of metabolic circuitry

The absence of the leptin surge or of functional leptin receptors, and changes to circulating ghrelin and insulin levels, results in suppressed to near-absent neurite

growth between these regions. These effects can lead to lifelong deficits in satiety and metabolic signalling and pronounced obesity (Bouret *et al.* 2004b, Steculorum *et al.* 2015). Ob/ob mice that do not produce leptin are obese compared with controls of the same age and have a substantially reduced density of fibres projecting from the ARC to the PVN and other regions of the hypothalamus (Bouret *et al.* 2004b). The obese phenotype and the fibre density can be rescued by exogenous leptin given between P4 to P12, but not when leptin is given in adulthood (Bouret *et al.* 2004b, Vickers *et al.* 2005, Bouyer & Simerly 2013). In the mouse, the window within which leptin maintains neurotrophic potential closes around P28, with the duration of the leptin surge likely being important for this development; longer exposures to high leptin having greater neurotrophic potential (Kamitakahara *et al.* 2018). Early life events that perturb these hormone-based signals can thus have a lasting impact on this hypothalamic circuitry (Table 1).

Early life overfeeding, such as by suckling rat and mouse pups in small litters, elevates circulating leptin and also stimulates changes in methylation of the promoter regions for NPY (reduced methylation) and POMC (increased methylation) in the hypothalamus and reduces POMC expression (Lopez *et al.* 2005, Plagemann *et al.*

2009, Stefanidis & Spencer 2012). Neonatal overfeeding also induces acute changes in hypothalamic NPY and AgRP density, and an overweight phenotype that lasts beyond the period of overfeeding (Sominsky *et al.* 2017b). Similarly, maternal high-fat diet during lactation in mice reduces α -melanocyte-stimulating hormone (α -MSH) and AgRP fibre density in the PVN, DMH and LH of the offspring, and this is linked to hyperinsulinemia. Specific inactivation of the insulin receptor in POMC neurons rescues this effect and the negative consequences for glucose tolerance. Speaking to the importance of the postnatal period for this development in rodents, maternal high-fat diet and obesity prior to and during gestation does not alter hypothalamic connectivity in the offspring (Vogt *et al.* 2014). Likewise, leptin treatments after P28 in the mouse have no effect (Kamitakahara *et al.* 2018).

Non-nutritive challenges can also influence the hormonal profile during development and stimulate detrimental programming effects on this circuitry. Chronic early life stress is associated with an early reduction in weight gain (P2-P9) followed by a later weight acceleration (P14 onwards) such that the stressed pups have normal weight as adults, but accumulate more adipose when consuming a high-fat diet (Yam *et al.* 2017a). The effects of early life stress on ghrelin are sex

Table 1 Summary of key studies on perinatal programming of hypothalamic metabolic circuitry.

Model	Hormonal correlates	Obesity	Hypothalamic effects	Reference
Leptin deficiency – ob/ob	↓ leptin	✓	↓ ARC AgRP and α -MSH projections to PVN, DMH, LH	Bouret <i>et al.</i> (2004b)
Early life stress	↓ leptin	✓ transient then ↑ adipose with HFD	↑ ARC and PVN NPY, ↑ ARC AgRP fibre density	Yam <i>et al.</i> (2017a)
Maternal separation	↓ leptin	X	↑ NPY mRNA	Schmidt <i>et al.</i> (2006)
Foetal undernutrition	↓ responses to leptin	✓	↑ NPY and CART fibre density in PVN	Yura <i>et al.</i> (2005)
Neonatal overfeeding	↑ leptin	✓	↓ NPY, ↑ POMC promoter methylation. ↑ ARC AgRP and NPY density. ↓ PVN NPY density. Somewhat reversible	Lopez <i>et al.</i> (2005), Plagemann <i>et al.</i> (2009), Sominsky <i>et al.</i> (2017b)
Anti-ghrelin	↓ ghrelin action	✓	↑ ARC AgRP and α -MSH projections to PVN, DMH, LH	Steculorum <i>et al.</i> (2015)
Ghrelin	↑ ghrelin	✓	↓ ARC AgRP and α -MSH projections to PVN, DMH, LH	Steculorum <i>et al.</i> (2015)
Insulin implants	↑ insulin	✓	neuronal density ↑ in DMH, VMHpv, ↓ in VMHpf	Plagemann <i>et al.</i> (1992, 1999)
Maternal HFD – lactation	↑ insulin	✓	↓ α -MSH ↓ AgRP fibre density in PVN, DMH, LH	Vogt <i>et al.</i> (2014)
Maternal HFD prior to and during gestation (not lactation)	X	X	X	Vogt <i>et al.</i> (2014)

α -MSH, α -melanocyte-stimulating hormone; ARC, arcuate nucleus; AgRP, agouti-related protein; CART, cocaine- and amphetamine-regulated transcript; DMH, dorsomedial hypothalamus; HFD, high-fat diet; LH, lateral hypothalamus; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus of the hypothalamus; VMH, ventromedial hypothalamus (pv=ventrolateral, pd=dorsomedial).

dependent, suggesting that ghrelin does not influence feeding, metabolic or stress circuitry in this model, since other effects of early life stress on this circuitry are similar between the sexes (Yam *et al.* 2017b). However, early life stress does lead to a suppression of leptin that may be responsible for some of these long-term weight regulatory effects (Yam *et al.* 2017a).

While disruptions to weight regulation that ultimately lead to overweight and obesity are seen in early life stress and leptin suppression models, they seem to achieve this via opposing mechanisms to those of hyper-leptinemia. As such, leptin antagonists or leptin receptor polymorphisms prevent neurite growth in the hypothalamus and ultimately reduce the density of axonal projects between the ARC and other regions of the hypothalamus (Bouret *et al.* 2004b), while leptin suppression with maternal separation is linked to increased hypothalamic NPY mRNA (Schmidt *et al.* 2006) and leptin suppression with early life stress leads to increased PVN NPY and AgRP fibre density (Yam *et al.* 2017a,b). A premature leptin surge, as is seen with foetal undernutrition in the mouse, can also lead to increased density of NPY and CART terminals in the PVN, as well as leptin resistance and, again, an obese phenotype into adulthood (Yura *et al.* 2005). In similar fashion, both hyper- and hypo-ghrelinemia in postnatal life result in an overweight phenotype long term, despite opposite effects on the density of AgRP and α -MSH fibres in the PVN (Steculorum *et al.* 2015). It appears that any perturbation to the hypothalamic metabolic circuitry results, if anything, in an obese phenotype. This effect fits with the idea that maintaining adequate nutrition is a highly essential function for survival there is therefore substantial redundancy towards a drive to eat in this circuitry.

The timing for the development of this hypothalamic feeding circuitry, and its dependence upon leptin and ghrelin, has been relatively well established in the mouse. However, in the rat, the effects of both leptin and ghrelin seem to be less robust and permanent. In neonatally overfed rats, leptin is elevated about 14-fold in both males and females (Stefanidis & Spencer 2012); yet, this has only transient or no effects on density of NPY and AgRP fibres in the ARC and PVN. In males, neonatal overfeeding leads to an early increase in NPY/AgRP fibres in the ARC and an early resistance to leptin, both of which are resolved by adulthood although the elevated body weight remains (Sominsky *et al.* 2017b). Neonatal overfeeding in females has no effect on ARC or PVN AgRP, NPY or POMC and very minimal effects on leptin sensitivity (Ziko *et al.* 2017). Likewise, neonatal overfeeding affects circulating ghrelin

in the male rat, suppressing it rather than increasing it as it does in the mouse. However, its influence on ghrelin sensitivity is only transient, with normal responses to exogenous ghrelin seen in neonatally overfed adults (Sominsky *et al.* 2017a). It is noteworthy that even in the mouse, body weight and density of ARC axons are normal by P35 in ghrelin knockouts, indicating compensatory factors likely play a role in the case of disruptions to ghrelin signalling in early life (Steculorum *et al.* 2015).

Equating human and rodent developmental ages

Much of the literature addressing hypothalamic development comes from rodent (rat and mouse) studies. Although hypothalamic structure and function is highly conserved across species, equating developmental ages between animal models and humans is sometimes problematic and controversial. In the rat and mouse, the cytoarchitecture of the hypothalamus starts to develop at in mid-gestation, with neurogenesis followed by migration, axonal extension, dendritic arborisation and synaptogenesis all commencing prior to birth. There is then a second major developmental phase in the postnatal period, where the satiety and stress circuitry mature between approximately P6 and 16. In humans and non-human primates, the relative timing of hypothalamic development is the same, but the absolute timing of different developmental milestones occurs at different times across gestation. For example, the generation of specific cell types begins in the latter part of the first trimester (around 9 weeks) for early generated cells, such as those in the LH, whereas the majority of neurons (those in the POA, DMH, VMH, ARC and PVN) are generated throughout the second trimester (Koutcherov *et al.* 2002). Subsequent events – migration, axon extension, dendritic arborisation, synaptogenesis and a significant amount of circuit remodelling/elaboration – occur in the third trimester in humans. In rodents, this phase is split such that migration, as well as some axon extension, dendrite formation and synaptogenesis occur before birth and are followed by circuit remodelling and further synaptogenesis in the postnatal period (Koutcherov *et al.* 2003, Grayson *et al.* 2006). In terms of later development, the juvenile period in rats and mice is between three and six weeks of age, with puberty occurring around five to six weeks old. Adulthood is thus considered to be from around eight weeks onwards, with reproductive senescence between 15 and 20 months (females) and old age occurring between 24 and 36 months depending on strain (Sengupta 2013). If calculating a linear equivalence in adult rodents based

on lifespan, one could consider one day in the life of an adult rat to be approximately equivalent to one month in the life of a human (Sengupta 2013). However, this definition is less useful when assessing very short time frames, such as when examining responses to acute stress or satiety signals, and the temporal equivalence of medium-term metabolic challenges is also unclear. These caveats therefore need to be considered when comparing rodent developmental ages to those of humans.

Few studies have investigated the roles of these metabolic factors in human hypothalamic development, but there is evidence that ghrelin is low at birth in humans as it is in mice and rats and that it approximately doubles between birth and one month of age, peaking at the first two years of life and subsiding significantly towards the end of puberty (Soriano-Guillen *et al.* 2004a). Leptin levels in humans rise during pregnancy and subside after birth in the mother as well as the foetus and newborn, but the magnitude of the increase is not as high as in rodents and a postnatal (or prenatal) leptin surge has not been identified (reviewed in Valteau & Sullivan 2014). Whether changes to ghrelin and/or leptin in young humans affect the development of hypothalamic circuitry is not clear. Certainly, early weight gain is highly predictive of lifelong obesity (Whitaker *et al.* 1997, Stettler *et al.* 2005) and breast milk composition of some of these hormones is linked to rate of weight gain (Kon *et al.* 2014). There is also some evidence that ghrelin, at least, may correlate with measures of growth at term (≥ 37 weeks' gestation) but not earlier than this (Ng *et al.* 2005).

Stress circuitry

In humans, the HPA axis completes its maturation during the last trimester of pregnancy (Bolt *et al.* 2002). In rats and mice, the critical development of this circuitry occurs postnatally, during the first week of life (reviewed in Rao 2015). At this time, the rat and mouse hypothalamus is characterised by high *Crh* gene expression and lower glucocorticoid receptor gene expression that decrease and increase, respectively, as the animal approaches weaning age (Boullu-Ciocca *et al.* 2005). In this early postnatal phase, the pups are hypo-responsive to stress, having low circulating corticosterone and suppressed ACTH and corticosterone responses to mild psychological stress or immune challenge (Schmidt *et al.* 2006). This effect is likely one that is maintained by the presence of metabolic factors, including leptin and glucose that are usually obtained through regular suckling from the dam (Schmidt *et al.* 2006).

Perinatal programming of stress circuitry

The stress hypo-responsive period in rodents, and, thus, normal maturation of the HPA axis, can be disrupted by changes to metabolic factors. For instance, maternal separation leads to a reduction in pup circulating leptin and glucose, usually obtained from the dam, and an increase in ghrelin. These changes precede the increases in circulating corticosterone and HPA axis activation that signal the termination of the stress hypo-responsive period. Feeding pups during maternal separation can mitigate its effects (Rosenfeld *et al.* 1993, van Oers *et al.* 1998). A ghrelin antagonist, as well as replacement glucose, can also restore the corticosterone and ACTH towards their stress hypo-responsive levels (Schmidt *et al.* 2006). It is likely they do this by influencing the expression of CRH in the PVN, since *Crh* mRNA is reduced with maternal separation and restored with a ghrelin antagonist or glucose treatment (Schmidt *et al.* 2006). While no overt effects on weight gain have been reported from maternal separation experiments (and the ensuing reductions in circulating leptin), there is some evidence that satiety and feeding may be disrupted. Maternally separated rats weigh less into adulthood than controls and consume more palatable food. They are also more sensitive to the anorexigenic effects of cholecystokinin (McIntosh *et al.* 1999). Hypothalamic *Npy* mRNA is also increased by maternal separation (Schmidt *et al.* 2006).

Premature termination of the stress hypo-responsive period can lead to a hyper-responsive HPA axis long term. Thus, maternally separated rats have increased immobility in the forced swim (Lajud *et al.* 2012), elevated basal levels of stress hormones (Rots *et al.* 1996), and exacerbated anxiety and ACTH responses to a novel environment (Wigger & Neumann 1999) as adults. Again, these responses are somewhat sex dependent, with both sexes showing increased anxiety but only the males having exacerbated HPA axis responses (Wigger & Neumann 1999). Early life stress without maternal separation, in experimental animals and in humans, can also lead to exacerbated HPA axis responses to stress later in life. Thus, humans who experience extended periods in institutionalized care, neglect or abuse in early life demonstrate blunting of the normal cortisol rhythm (Gunnar *et al.* 2001), extremely high or low morning cortisol (Cicchetti & Rogosch 2001) and exacerbated cortisol responses to stress (Laurent *et al.* 2015). This latter effect is predictive of heightened anxiety (Laurent *et al.* 2015). In rats, chronic early life stress also leads to exacerbated HPA axis responses to stress (Yoshihara & Yawaka 2008, Yam *et al.* 2015). This is likely

due to hypothalamic alterations in CRH and CRFR2, its receptor, expression (Eghbal-Ahmadi *et al.* 1997, Schmidt *et al.* 2004) and also to epigenetic modifications to the glucocorticoid and mineralocorticoid receptors in the hypothalamus and elsewhere in the brain. For example, Meaney and colleagues have shown maternal attention suppresses HPA axis responses to stress throughout life via maternal contact-mediated changes in histone acetylation and NGF1-A binding to the glucocorticoid receptor promoter to increase expression of this receptor and enhance the efficiency of glucocorticoid-negative feedback (Weaver *et al.* 2004a).

Neonatal overfeeding can also interrupt normal HPA axis development, prematurely elevating circulating glucocorticoids, ACTH and hypothalamic glucocorticoid receptor expression, as well as reducing hypothalamic *Crh* mRNA (Boullu-Ciocca *et al.* 2005). These effects are linked to exacerbated HPA axis responses to immune challenge long term in both males and females that were overfed as neonates (Clarke *et al.* 2012), and exacerbated responses to psychological stress in females (Spencer & Tilbrook 2009).

Reproductive circuitry

Central reproductive circuitry is established predominantly prenatally (reviewed in Franceschini & Desroziers 2013), but substantial changes in the expression and function of this circuitry occur postnatally, particularly during the peripubertal period, since activation of the GnRH neurons is critical for the initiation of puberty (Plant & Barker-Gibb 2004). This activation is thought to be driven by kisspeptin neurons within the hypothalamus that are central to the onset and progression of puberty (Terasawa *et al.* 2013).

In rodents, expression of kisspeptin neurons in the AVPV increases dramatically postnatally (Navarro *et al.* 2004, Han *et al.* 2005). In rats, no kisspeptin neurons are detected in the AVPV at P10. However, by the initiation of puberty, their expression rapidly reaches adult-like levels, in both sexes, accompanied by the development of kisspeptin projections to GnRH neurons (Clarkson & Herbison 2006). These postnatal changes in kisspeptin expression within the AVPV are dependent upon the increasing levels of estradiol (Clarkson *et al.* 2009, Takase *et al.* 2009). There is thus a substantial sex difference in the expression of kisspeptin neurons, with females expressing significantly more of these in the AVPV in mice (Clarkson & Herbison 2006) and in the AVPV and ARC in rats (Takumi *et al.* 2011) than males. This sex difference

is particularly significant given that the population of kisspeptin neurons in this region sends direct projections to GnRH neuronal cell bodies in the POA (Yip *et al.* 2015). These postnatal temporal and spatial changes in the expression of kisspeptin suggest that pubertal development is initiated by the population of ARC kisspeptin neurons and is followed by an estradiol-dependent activation of AVPV kisspeptin neurons triggering the GnRH release.

As with rodents, in non-human primates, the hypothalamic content of kisspeptin and its receptor increase in the prepubertal period (Shahab *et al.* 2005, Keen *et al.* 2008). This pattern occurs in parallel to the peripubertal increase in GnRH release (Watanabe & Terasawa 1989). This pubertal increase in kisspeptin signalling is, however, independent of the concomitant increase in circulating estradiol in primates, and is not likely to drive increased pubertal GnRH release but rather mediates the reduction in GABA inhibition of GnRH neurons (Guerriero *et al.* 2012, Kurian *et al.* 2012). In primates, GnRH pulsatility is increased after birth and this is followed by a decline in late infancy and during juvenile development, maintaining gonadal quiescence until the onset of puberty (Plant & Witchel 2006, Terasawa & Kurian 2012). This suppression of GnRH release is mediated by an inhibitory GABAergic tone, and the reduction of GABA inhibition reactivates GnRH pulsatility and triggers puberty (Terasawa 2005). In contrast to primates, postnatal GnRH release in rodents is negligible and its levels increase prior to puberty, likely reflective of the final stages of maturation of the GnRH circuitry rather than the reactivation of the prenatally established circuitry that occurs in primates (Plant 2015).

Perinatal programming of reproductive circuitry

Pubertal maturation in all species is highly dependent on the ability of an organism to maintain adequate energy balance and varying metabolic conditions play pivotal role in determining the timing of puberty onset (Sanchez-Garrido & Tena-Sempere 2013). Therefore, poor dietary conditions during gestation and/or postnatal development that alter the development of metabolic circuitry and change the availability of circulating metabolic hormones have also been shown to not only change the timing of puberty but, at times, to program long-term alterations in hypothalamic reproductive functionality. Of the major metabolic hormones, leptin and ghrelin have received significant attention as primary candidates linking metabolic status and hypothalamic reproductive signalling.

Leptin has long been recognised as a major permissive signal for the onset of puberty, especially in females (Cheung *et al.* 1997). Ob/ob mice do not undergo puberty and are infertile and a normal phenotype is restored by chronic leptin treatment (Barash *et al.* 1996, Chehab *et al.* 1996). Similarly, in human patients with congenital leptin deficiency, pubertal development is restored by leptin treatment (Farooqi *et al.* 1999, 2002). Leptin also promotes pubertal development in normal rats and mice (Ahima *et al.* 1997, Chehab *et al.* 1997, Cheung *et al.* 1997), and leptin levels are inversely correlated with the age at menarche in pubertal girls (Matkovic *et al.* 1997).

Leptin's actions on GnRH pulsatility leading to puberty onset are indirect. Immunohistochemical analyses of the mouse and sheep brain have confirmed that while there are populations of leptin receptor expressing neurons in the ventral premammillary nucleus of the hypothalamus and POA, leptin receptor is not expressed by GnRH neurons nor by AVPV kisspeptin neurons (Louis *et al.* 2011). Leptin thus stimulates a distinct population of Ob-Rb-expressing neurons in the ventral premammillary nucleus of the hypothalamus to induce GnRH release from the POA (Donato *et al.* 2011).

Ghrelin's actions on GnRH/luteinising hormone release and puberty onset are predominantly inhibitory, and males appear to be more susceptible to this inhibitory effect of ghrelin pre-puberty than females (Fernandez-Fernandez *et al.* 2004, 2005, 2007, Martini *et al.* 2006). Fasting, as well as acute ghrelin administration, significantly reduce *Kiss1* mRNA expression in the POA (Forbes *et al.* 2009). However, there is no evidence for the expression of the ghrelin receptor (growth hormone secretagogue receptor, GHSR) on GnRH, kisspeptin or RFamide-related peptide neurons (Smith *et al.* 2013). The vast majority of hypothalamic GHSR-expressing neurons express estrogen receptor (ER) α , suggesting the inhibitory action of ghrelin on GnRH release is likely to be mediated by estradiol (Smith *et al.* 2013, Frazao *et al.* 2014). In humans, circulating ghrelin is significantly increased in early childhood and these levels then subside by puberty (Whatmore *et al.* 2003, Soriano-Guillen *et al.* 2004b). The influence of the pre-pubertal decline in ghrelin on earlier puberty onset is particularly pronounced in boys (Whatmore *et al.* 2003), suggesting that under normal conditions, the falling ghrelin levels during the peripubertal period may act as a permissive metabolic signal on puberty, while under pathological conditions, such as in boys with constitutional delay of growth and puberty, ghrelin levels are significantly increased and are

negatively correlated with measures of body weight and height (El-Eshmawy *et al.* 2010, Sen *et al.* 2010).

Regardless of the mode of leptin and ghrelin's actions on the hypothalamic GnRH pulse generator, multiple studies have demonstrated that perinatal diet alters the timing of puberty onset and impairs ovulation in the offspring, indicating a dysregulation of the hypothalamic reproductive circuitry. In children, excess adiposity in early childhood in girls is typically linked to advanced puberty, while pubertal development in obese boys appears to be delayed. Childhood obesity in both sexes, however, predisposes to significant reproductive dysfunction in adulthood (reviewed in Burt Solorzano & McCartney 2010). A tendency for earlier pubarche has also been identified in girls born to mothers who were obese and/or suffered from gestational diabetes mellitus (Kubo *et al.* 2016). In rats, consumption of high-fat diet during pregnancy and lactation is associated with the advancement of puberty and irregular oestrous cyclicity in adult female offspring, indicative of early reproductive senescence (Sloboda *et al.* 2009, Connor *et al.* 2012). Early life overfeeding is also associated with increased postnatal body weight and earlier age at vaginal opening in rats and mice (Caron *et al.* 2012, Smith & Spencer 2012), along with a persistent increase in the levels of leptin (Castellano *et al.* 2011, Sominsky *et al.* 2016) and a significant decline in circulating ghrelin pre-puberty (Colden *et al.* 2015). A pubertal increase in the hypothalamic expression of kisspeptin has also been shown in the neonatally overfed in one (Castellano *et al.* 2011), but not other studies (Caron *et al.* 2012, Smith & Spencer 2012), possibly due to differences in the timing of observations. In contrast, neonatally overfed females have a reduction in prepubertal ARC-derived kisspeptin fibres (Caron *et al.* 2012).

Insufficient energy reserve and calorie restriction pre- and postnatally are also known to produce long-term negative effects on hypothalamically-mediated pubertal development and adult reproductive function. The onset of puberty is typically delayed in males and females that experienced maternal undernutrition or intrauterine growth restriction (Engelbregt *et al.* 2000, Rae *et al.* 2002, Leonhardt *et al.* 2003, Guzman *et al.* 2006). Despite rapid postnatal catch-up growth and significantly increased circulating leptin levels, female offspring of undernourished dams show decreased hypothalamic expression of *Kiss1* mRNA that may contribute to delayed puberty (Iwasa *et al.* 2010). Similarly, postnatal undernutrition delays pubertal development (Caron *et al.* 2012, Smith & Spencer 2012). While the delay in puberty onset in undernourished males has been associated with

changes in circulating testosterone and estradiol, but not with hypothalamic *Kiss1* mRNA expression (Smith & Spencer 2012), neonatally underfed females show impaired development of axonal projections from the ARC to the POA pre-puberty, leading to a reduction in the density of kisspeptin fibres in the POA that is maintained into adulthood (Caron *et al.* 2012). Both undernutrition and overfeeding during the first three weeks of postnatal life lead to reduced reproductive performance in adulthood, with fewer litters being born to these mice than in controls (Caron *et al.* 2012).

Poor maternal care and increased perinatal stress similarly predict changes in the timing of puberty onset in the offspring. Michael Meaney's group has shown that prenatal stress induced by low-quality maternal care predicts early puberty onset, but, interestingly, also higher sexual receptivity and increased fecundity. In adulthood, these female offspring also have increased proestrous levels of luteinizing hormone and progesterone, and these changes are likely mediated by the increased expression of ER α in the AVPV (Cameron *et al.* 2008). These data highlight the potential adaptation of reproductive strategies to environmental conditions. Since limited allocation of parental care is likely to be reflective of limited resources, advanced reproductive development and increased motivation to mate aim to compensate for the higher risk of mortality and thus favour increased quantity of offspring, rather than optimal quality (Cameron 2011).

Adult hypothalamic development

The prenatal, early postnatal and pubertal periods are important phases for hypothalamic development that are particularly vulnerable to environmental influence. However, it is now clear that the hypothalamus, and, indeed, the brain as a whole, continues to change throughout life and into old age. In addition to the two canonical sites of adult neurogenesis, the hippocampal subgranular zone and the subventricular zone of the lateral ventricle, several other regions throughout the brain, including hypothalamus, are now known to display neurogenesis and gliogenesis in response to specific stimuli (Migaud *et al.* 2016). Hypothalamic tanycytes that line the base of the third ventricle at the median eminence are a key neurogenic population that give rise to functional neurons throughout early postnatal and adult life (Lee *et al.* 2012) and into old age (Chaker *et al.* 2016). Evidence suggests that new hypothalamic neurons

both respond to and regulate key hypothalamic functions including satiety and energy balance, stress responses and reproduction. For instance, inhibition of neural stem cell proliferation or ablation of neural stem cells leads to changes in weight gain and energy expenditure in the mouse and chronic high-fat diet can affect neural stem cell survival and rate of proliferation (Lee *et al.* 2012, Li *et al.* 2012). Whether neural stem cell proliferation is enhanced or suppressed by high-fat diet and whether this contributes to weight gain or loss is, however, yet unclear as studies have illustrated changes in both directions and with some sex dependency (Lee *et al.* 2012, Li *et al.* 2012, Blackshaw *et al.* 2016). As with neurons involved in metabolic function, those involved in the reproductive circuitry also continue to be produced throughout life, even in older animals (mice of 16 months) (Chaker *et al.* 2016). Furthermore, inhibiting cell proliferation in this region can suppress the luteinizing hormone surge necessary to stimulate ovulation (Mohr *et al.* 2017). Adult hypothalamic neurogenesis is regulated by insulin-like growth factors (IGF) and other circulating hormones (Bless *et al.* 2014, Chaker *et al.* 2016), with conditional ablation of the IGF receptor from hypothalamic stem cells elevating neuronal production (Chaker *et al.* 2016). Thus, environmental stimuli that influence neurogenesis can continue to contribute to hypothalamic development throughout life.

The adult hypothalamus is also subject to environmental influence guiding synaptogenesis. For instance, in the rat and primate brain, there is a reversible loss of up to 50% of axosomatic synapses in the ARC that precedes the preovulatory luteinizing hormone surge each cycle, and this loss is reversed by the morning of metestrous (Olmos *et al.* 1989, Witkin *et al.* 1991, Zarnovszky *et al.* 2001). This synaptic remodelling is regulated by cyclical fluctuations in estradiol, since estradiol immunoneutralisation prevents synaptic retraction in the ARC, blocks the positive feedback of estradiol and prevents the ovulatory luteinizing hormone surge (Naftolin *et al.* 1996). The fluctuating levels of IGF1 in the ARC are also implicated in estradiol-induced synaptic remodelling, and IGF1 receptor activation appears to be necessary for the synaptic plasticity seen during the estrous cycle (Fernandez-Galaz *et al.* 1999). During aging, female rodents lose this synaptic plasticity in the ARC and cease to respond to the mid-cycle estrogen-induced gonadotropin surge, entering constant vaginal oestrous. These effects are mimicked by ovariectomy and can be reversed by estradiol supplementation (Hung *et al.* 2003). Similar to estradiol, leptin regulates hypothalamic synaptic plasticity and both

estradiol and leptin remodel the excitatory synaptic input to POMC neurons in the ARC. While estradiol's effects on POMC neurons are independent of leptin and its receptor (Gao *et al.* 2007), estradiol activates a STAT3-dependent pathway (Bjornstrom & Sjoberg 2002) and increases leptin-induced STAT3 phosphorylation in the ARC (Clegg *et al.* 2006), implicating the STAT3 pathway in estradiol-induced synaptogenesis. Independently, exogenous leptin can restore the deficits in numbers of synapses onto NPY and POMC cells in ob/ob mice, also restoring the balance between excitatory and inhibitory synapses and the functional activity of these neurons (Pinto *et al.* 2004). Exogenous ghrelin has a similar ability to cause dynamic changes in hypothalamic synaptic density and function, in this case, decreasing excitatory and inhibitory synaptic inputs onto POMC cells in an effect consistent with ghrelin's orexigenic function (Pinto *et al.* 2004). At least in the case of leptin, this effect may be mediated by increases in the expression of brain-derived neurotrophic factor (Komori *et al.* 2006). These findings suggest leptin and ghrelin may modulate synaptogenesis in accordance with metabolic need, at least in larger doses under pathological conditions (ob/ob mice). Whether dietary manipulations can acutely drive these effects in healthy animals remains to be seen. However, long-term diet-induced obesity in adult mice leads to synaptic attrition in those vulnerable to the obesity-inducing effects of the diet, as well as a failure to increase inhibitory synapses such as is seen in obesity-resistant individuals (Horvath *et al.* 2010).

In addition to hypothalamic neurogenesis and synaptogenesis, environmental stimuli can also influence the epigenome. It has been identified for some time that significant life stress, including war trauma, or abuse, even in adulthood, can lead to changes in methylation of the promoter for the glucocorticoid receptor. The majority of human studies on this topic have relied upon blood or saliva to assess epigenetic changes in hypothalamic-relevant genes. Thus, there is a link between epigenetic changes to salivary glucocorticoid receptor and memory dysfunction in post-traumatic stress disorder (PTSD). Male survivors of genocidal war with higher glucocorticoid receptor promoter DNA methylation report fewer instances of intrusive memories (Vukojevic *et al.* 2014). As such, reduced methylation at the glucocorticoid receptor promoter is likely to account for higher expression of the receptor and a vulnerability to PTSD (Yehuda *et al.* 2015). Meaney and colleagues have shown this mechanism is important centrally with methylation at *Ngf1a* affecting transcription of the glucocorticoid receptor and thus HPA axis reactivity at the

level of the hippocampus as a consequence of variations in maternal attention (Weaver *et al.* 2004a,b). While these studies focussed on the hippocampus, methylation at the level of the hypothalamus also appears important for regulating transcription of the glucocorticoid receptor in this region, at least in that promoter 1, methylation levels are inversely correlated with glucocorticoid receptor transcription. However, chronic stress has no effect on PVN methylation or glucocorticoid receptor expression, despite effects at pituitary and adrenal (Witzmann *et al.* 2012). Thus, DNA methylation patterns are variable and vulnerable to challenge throughout life, but more work is needed to elucidate specific hypothalamic effects.

Conclusions

The hypothalamus plays a major role in the homeostatic control of metabolism, stress responsiveness, central reproductive function, as well as in thermoregulation, sleep and other biological processes. While several structural and functional components of the hypothalamic neuronal network are laid down prenatally, these circuitries undergo further extensive development and fine tuning postnatally. As such, the establishment of the metabolic circuitry is guided by the fluctuation in major metabolic hormones, leptin and ghrelin; the maturation of the stress hypothalamic circuitry is driven by the rise in circulating glucocorticoids; and, AVPV and ARC reproductive circuitry change rapidly postnatally, to attain their adult functionality at puberty, which, in females, is marked by the establishment of pulsatile pattern of GnRH release. Considering the functional and anatomical interconnections among these networks, it may not be surprising that similar environmental influences can trigger changes in their establishment and functionality. As such, alterations in the levels of metabolic, stress and reproductive hormones, or varied nutritional supply during early development, may change the normal developmental trajectory of the hypothalamus, altering the developing, and, consequently, the adult brain. Although the perinatal period of life is undoubtedly the most vulnerable to environmental influences, the adult brain is not protected from harm, with exposure to poor diet or extreme stress inducing significant changes in hypothalamic neuronal connectivity, through changes in neurogenesis and the epigenome. Hypothalamic synaptic plasticity, significantly pronounced in the female brain, is highly dependent on the exposure to sex steroids and is thus lost at reproductive senescence, inducing further

changes in the central control of energy balance and adiposity.

The development of the hypothalamus throughout life is sex specific to a degree. There does not appear to be sexual dimorphism in the timing of hypothalamic development (Kamitakahara et al. 2018). However, sensitivity to environmental effects may differ between males and females. Thus, female ob/ob mice are more responsive than males to the restorative effects of leptin on AgRP innervation of the hypothalamus (Kamitakahara et al. 2018). Unlike males, female rats are also not susceptible to the hypothalamic re-organisation effects of neonatal overfeeding (Ziko et al. 2017), suggesting a degree of resilience in this sex. This effect is likely related to sex differences in sensitivity to gonadal hormones, since ARC neurons express androgen receptors and ER α at these early ages (Kamitakahara et al. 2018) and hypothalamic neurons are sensitive to exposure to sex steroids in the first weeks of life (Waters & Simerly 2009). There are also evident species differences in hypothalamic development. Humans, for instance, may not have a developmental leptin surge as rodents do (Valleau & Sullivan 2014). Rats and mice both display a leptin surge that is important for establishing metabolic hypothalamic connectivity (Ahima et al. 1998, Delahaye et al. 2008) and both display similar temporal changes in hormones and gene expression relevant for stress and reproductive circuitry (Walker et al. 1997, Boullu-Ciocca et al. 2005, Castellano et al. 2011, Caron et al. 2012). However, while perturbations in leptin and ghrelin during development can permanently disrupt hypothalamic connections and weight regulation in mice (e.g. (Bouret et al. 2004b, Steculorum et al. 2015)), the effects are somewhat reversible in rats (Sominsky et al. 2017a,b), suggesting compensatory mechanisms may be at play.

Despite sex and species, though, it is important to remember that this continuous plasticity of the brain, including the hypothalamus, holds a unique key to our ability to improve or reverse the negative influences we have experienced throughout our life. For instance, lifestyle changes, such as exercise and weight loss, are showing promising effects in improving hypothalamic metabolic function in the obese (Laing et al. 2016). Similarly, weight loss appears to be beneficial for obese women who suffer infertility and hypothalamic amenorrhea (Clark et al. 1995), and enriched environment in adolescence has been shown to reverse the effects of prenatal stress by normalising HPA axis stress reactivity (Morley-Fletcher et al. 2003). Our own findings show that changes in the development of hypothalamic metabolic connectivity

induced by postnatal overfeeding in rats are resolved by adulthood, when animals are placed on a normal chow diet (Sominsky et al. 2017b). Overall, these encouraging data suggest that while severe disruption of hypothalamic development has detrimental consequences on a range of biological processes, milder influences may have a transient effect that at times can be reversed.

Declaration of interest

The authors declare that they have no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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