REVIEW

Liver at the nexus of rat postnatal HPA axis maturation and sexual dimorphism

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Abstract

Normal function of the hypothalamic–pituitary–adrenal (HPA) axis is critical for survival, and its development is choreographed for age-, sex- and context-specific actions. The liver influences HPA ontogeny, integrating diverse endocrine signals that inhibit or activate its development. This review examines how developmental changes in the expression of genes in the liver coordinate postnatal changes in multiple endocrine systems that facilitate the maturation and sexual dimorphism of the rat HPA axis. Specifically, it examines how the ontogeny of testicular androgen production, somatostatin-growth hormone activities, and hypothalamic-pituitary-thyroid axis activity intersect to influence the hepatic gene expression of insulin-like growth factor 1, corticosteroid-binding globulin, thyroxine-binding globulin, 11 β -hydroxysteroid dehydrogenase type 1 and 5 α -reductase type 1. The timing of such molecular changes vary between mammalian species, but they are evolutionarily conserved and are poised to control homeostasis broadly, especially during adversity. Importantly, with the liver as their nexus, these diverse endocrine systems establish the fundamental organization of the HPA axis throughout postnatal development, and thereby ultimately determine the actions of glucocorticoids during adulthood.

Key Words

- ▶ glucocorticoids
- ▶ sexual dimorphism
- ▶ corticosteroid-binding globulin
- ▶ thyroxine-binding globulin
- ▶ thyroid hormone
- ▶ growth hormone
- ▶ somatostatin
- ▶ insulin-like growth factor 1
- ▶ sex steroids
- ▶ 11 β -hydroxysteroid dehydrogenase type 1
- ▶ 5 α -reductase type 1

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Introduction

As a critical regulator of metabolic homeostasis, the liver senses and integrates hormone signals triggered by alterations in metabolism and/or physiological state in terrestrial vertebrates. Hepatocytes respond to these changes by modifying their intrinsic metabolic activity, as well as the production of plasma proteins that in turn affects nutrient delivery and the activity of multiple endocrine regulatory systems. Many hepatic genes that control these responses are themselves hormone-dependent, and are directly or indirectly controlled by factors such as growth hormone (GH), insulin-like growth factor 1 (IGF1), thyroid hormones and steroids; and in particular, the glucocorticoid hormones that govern

hepatic gluconeogenesis and glucose availability in the brain and other tissues (Loria *et al.* 2009).

Glucocorticoid hormones are steroids produced by the adrenal gland that regulate metabolic and homeostatic mechanisms throughout the body (Patel *et al.* 2014), control inflammation (Kadmiel & Cidlowski 2013), support reproduction (Whirledge & Cidlowski 2013) and modulate stress-related behaviors (Myers *et al.* 2014). Their actions have been studied extensively in relation to normal developmental trajectories in humans and other mammals, and abnormal glucocorticoid exposures during fetal or neonatal life have profound health outcomes in adulthood (Maniam *et al.* 2014, McGowan & Matthews

2018). Normal function of the hypothalamic–pituitary–adrenal (HPA) axis, which controls the plasma levels of glucocorticoids, establishes healthy metabolic function and stress responsivity later in life, and this is influenced by diverse stimuli including maternal care, diet, immune challenge, and stress (Maniam *et al.* 2014, Buschdorf & Meaney 2015). Furthermore, differences in the regulation of glucocorticoid action have been linked to sex disparities in inflammatory responses in rats (Duma *et al.* 2010), as well as the risk for inflammatory diseases, stress-related disorders and metabolic syndrome in humans (Bourke *et al.* 2012).

The timing of HPA axis maturation varies across mammals (Pryce 2008), since some species (e.g. primates, sheep, guinea pigs) undergo neuroendocrine maturation *in utero* while in others (e.g. rats, mice, rabbits) this occurs postnatally (Dobbing & Sands 1979, Dent *et al.* 2000). Despite species differences in the ontogeny of HPA axis maturation, the fundamental organization of the HPA axis and the roles of glucocorticoids in the maturation and function of most organ systems are shared across mammalian species, including rodents and humans (Herman *et al.* 2016), making the rat a valuable model for developmental study. This review discusses the role of the liver in coordinating the activities of several endocrine systems during postnatal development in the rat and how they intersect to promote the maturation of the HPA axis. Importantly, it advances a paradigm for how the liver acts to integrate these endocrine networks that are shared across mammalian species.

HPA axis

The HPA axis is a neuroendocrine system that operates between the hypothalamus, anterior pituitary, and adrenal glands to regulate plasma glucocorticoid levels. In the hypothalamus, neurosecretory neurons respond to aversive stimuli such as emotional or physical stress, for example, injury, infection, inflammation, or metabolic imbalance, as well as non-aversive stimuli such as circadian cues, by secreting corticotropin-releasing hormone (CRH) and arginine vasopressin. These neuropeptides are transported *via* the hypophyseal portal veins to the anterior pituitary where they stimulate adrenocorticotrophs to release adrenocorticotrophic hormone (ACTH), which in turn stimulates steroidogenesis in the adrenal gland to produce predominantly corticosterone in the rat, and cortisol in humans (Keller-Wood 2015). The HPA axis is self-regulated by glucocorticoids in a negative feedback manner through glucocorticoid-sensitive CRH

neurons in the hypothalamus and pro-opiomelanocortin (POMC)-producing adrenocorticotrophs in the pituitary (Gjerstad *et al.* 2018). Intra-adrenal glucocorticoid-mediated negative feedback has also been described (Spiga *et al.* 2017).

Plasma CBG levels set HPA axis tone

Prior to exerting their effects in target cells (de Kloet *et al.* 2019), the activities of glucocorticoids are controlled at two key levels: by binding to CBG in the blood circulation (Hammond 2016), and through enzymatic activation or inactivation in their target cells (Chapman *et al.* 2013).

Plasma CBG is produced by hepatocytes and is a serine protease inhibitor (SERPIN) family member (Hammond *et al.* 1987) encoded by *SerpinA6* in rodents. Plasma CBG binds glucocorticoids with high affinity, controlling the blood levels of these hormones by reducing their metabolic clearance (Siiteri *et al.* 1982), thereby serving as the main determinant of glucocorticoid levels (Bolton *et al.* 2014). However, CBG also regulates the amounts of these hormones that are not bound by plasma proteins and are free to diffuse through the plasma membranes of their target cells (Mendel 1989, Perogamvros *et al.* 2012). Once inside cells, glucocorticoids activate the intracellular mineralocorticoid receptor (MR) or glucocorticoid receptor (GR) and regulate glucocorticoid-dependent target genes (Reul *et al.* 2015, Spiga & Lightman 2015, de Kloet *et al.* 2019). Importantly, it is widely assumed that it is the ‘free’ corticosterone fraction rather than ‘total’ corticosterone, that is responsible for the HPA negative feedback in the brain.

Differences in plasma CBG concentrations between species and sexes are important to understand because they have wider implications on HPA tone (Table 1). In humans, the plasma concentrations of CBG (~500 nM) and cortisol (~50–500 nM over the circadian rhythm) are similar between sexes at all ages (Robinson *et al.* 1985, Russell & Lightman 2019). During physical trauma in humans, plasma cortisol increases to levels of ~800 nM (Gibbison *et al.* 2015), which far exceeds the cortisol-binding capacity of CBG, especially since plasma CBG levels generally decrease under pathological conditions (Hammond 2016). During psychological stress, CBG levels are not expected to change, while salivary cortisol levels as a surrogate measure of free plasma cortisol levels increase ~10-fold, again implying that plasma cortisol levels overshoot CBG levels by a large margin (Deinzer *et al.* 1997). In mice, plasma CBG (~200 nM in

Table 1 Basal and stress levels of CBG and corticosterone in human, mouse and rat.

	Plasma levels (nM)					
	Basal conditions			Stress conditions		
	Human	Mouse (C57Bl/6)	Rat (Wistar)	Human	Mouse (C57Bl/6)	Rat (Wistar)
Male CBG	500 ¹	250 ⁴	800 ⁶	300 ^{3*}	250 ⁵	800 ⁶
Female CBG	500 ¹	500 ⁴	1,200 ⁶	300 ^{3*}	500 ⁵	1,200 ⁶
Male CORT	50–500 ^{2,3}	20–80 ^{4,5}	1–150 ⁷	800 ^{2,3}	250 ^{4,5}	900 ⁶
Female CORT	50–500 ^{2,3}	40–160 ^{4,5}	15–350 ⁷	800 ^{2,3}	500 ^{4,5}	1,600 ⁶

*Based on a ~30–50% reduction in plasma CBG levels observed after cardiac surgery. ¹Robinson *et al.* (1985), ²Russell & Lightman (2019), ³Gibbison *et al.* (2015), ⁴Adams *et al.* (2015), ⁵Minni *et al.* (2014), ⁶Tinnikov (1999), ⁷Seale *et al.* (2004).

CBG, corticosteroid-binding globulin; CORT, corticosterone.

males, ~400 nM in females) and corticosterone (~20–80 nM in males, ~40–160 nM in females, over the circadian rhythm) differ between sexes, but their concentrations approximate those seen in humans, and corticosterone levels also increase to approach or exceed those of CBG under stress conditions (Minni *et al.* 2014, Adams *et al.* 2015). As in mice, plasma CBG levels in rats (~800 nM in males, ~1200 nM in females) are clearly sexually dimorphic (Gala & Westphal 1965), but they far exceed those of corticosterone (~1–150 nM in males, ~15–350 nM in females, over circadian rhythm) in the circulation (Seale *et al.* 2004). Therefore, substantial increases in adrenal corticosterone output are required during stress (reaching ~900 nM in males, ~1600 nM in females) to increase free corticosterone levels, especially in female rats because they have more CBG binding sites to occupy (Tinnikov 1999). Reports that plasma CBG does not follow a circadian rhythm in humans or rats (D'Agostino & Henning 1982a, Windle *et al.* 1998, Chung *et al.* 2016) are consistent with its relatively long plasma half-life of ~14.5 h (Smith & Hammond 1991).

In rats, strain differences in HPA axis activity correlate with differences in plasma CBG levels; Fischer 344 rats show higher diurnal and stress corticosterone levels than do Sprague Dawley or Lewis strains, but have higher plasma CBG levels (Dhabhar *et al.* 1993). Importantly, these strain differences predict an underlying influence of CBG to normalize glucocorticoid receptor occupancy in neural tissue. Differences in HPA axis activity and plasma CBG levels have also been reported across mouse strains (Cabib *et al.* 1990, Orava *et al.* 1994, Thoeninger *et al.* 2007), however their relationship has not been investigated. Notably, two C57Bl/6 mouse lines bred for 'low' and 'high' corticosterone responses to stress had CBG levels that explained this difference (Mattos *et al.* 2013), demonstrating again how CBG levels determine corticosterone levels and subsequently HPA axis tone.

It is, therefore, evident that the HPA axis in rats is more effectively buffered by CBG from fluctuations in corticosterone compared to the human and mouse. Furthermore, it follows that HPA tone is determined by the level of plasma CBG because female rodents not only have greater CBG levels than do males but they also have higher corticosterone levels, and it is not surprising that adrenal size, especially of the *zona fasciculata*, is larger in females compared to the male to furnish a greater corticosterone output (Sencar-Cupovic & Milkovic 1976). Thus, plasma CBG levels set by the liver determine the drive on the HPA axis required to normalize steroid exposure or deliver physiologically relevant concentrations of glucocorticoid.

Hepatic enzymes set HPA axis tone

The liver is the primary site of glucocorticoid clearance, and this function is critical in setting HPA tone. For example, impaired glucocorticoid clearance caused by liver disease results in adrenal insufficiency and suppression of the HPA axis (McNeilly *et al.* 2010). Two major hepatic glucocorticoid-metabolizing enzymes contribute to HPA tone in this way: 11 β -hydroxysteroid dehydrogenase type 1 (HSD11B1) and hepatic 5 α -reductase type 1 (SRD5A1). Metabolic transformations mediated by these hepatic enzymes influence both plasma and intracellular levels of glucocorticoids that can interact with glucocorticoid or mineralocorticoid receptors within their target cells (Chapman *et al.* 2013, Crowley *et al.* 2014). Hepatic HSD11B1 is particularly important in setting HPA axis tone as it contributes to plasma cortisol levels in humans by regenerating cortisol from its inert metabolite cortisone, and similarly in rodents through the conversion of 11-dehydrocorticosterone to corticosterone (Chapman *et al.* 2013). Acting in opposition, hepatic SRD5A1 irreversibly inactivates glucocorticoids to facilitate their clearance (Crowley *et al.* 2014). Deficiencies in either of these liver enzymes impact

HPA axis dynamics in mice (Kotelevtsev *et al.* 1997, Harris *et al.* 2001, Paterson *et al.* 2007, Livingstone *et al.* 2014) and likely have important roles in the development and maturation of the HPA axis in rats and humans, as will be discussed in more detail below.

Early postnatal development (postnatal days 1–15): androgen imprinting and HPT axis maturation

Interactions between the liver and several endocrine systems are already evident during the first 2 weeks of postnatal life in rats. During this time, testicular testosterone organizes hypothalamic somatostatin (SST) and growth hormone-releasing hormone (GHRH) neurons

that influence the liver later in development, and the hypothalamic-pituitary-thyroid (HPT) axis develops as a result of increased hepatic thyroxine-binding globulin (TBG) production (Fig. 1). The ontogenic changes in these systems as it pertains to the HPA axis are as follows.

Neonatal testosterone programs pituitary growth hormone release

In the hours following birth, male rats experience a surge of testosterone that exerts a multitude of organizational effects in the hypothalamus and pituitary, including that on GH-secreting somatotrophs (Murray *et al.* 1999, Chowen *et al.* 2004). The release of GH is regulated by the dynamic actions of hypothalamic GHRH and SST, which act to stimulate and inhibit GH release from the anterior

Figure 1

Early postnatal development: androgen imprinting and HPT maturation. Three endocrine axes that interact with the liver are highlighted by color: SST-GH-T (green), HPT (orange), and HPA (purple). Charts depict plasma levels of key components with respect to postnatal age in males (solid line) and females (dashed line). During postnatal days 1–15, neonatal exposure of males to testosterone programs hypothalamic GHRH and SST neurons in a sexually dimorphic manner that will become apparent during puberty. The HPT axis matures rapidly in both sexes due to increases in hepatic TBG production that drive increases in thyroid hormone levels. Sub-threshold levels of thyroid hormone, IGF1 and HSD11B1 may explain low plasma CBG levels during this time, which in turn explains low CORT levels in both sexes. HPT, hypothalamic-pituitary-thyroid; HPA, hypothalamic-pituitary-adrenal; PD, postnatal day; GH, growth hormone; TBG, thyroxine-binding globulin; T4, thyroxine; T, testosterone; CBG, corticosteroid-binding globulin; CORT, corticosterone; GHRH, growth hormone releasing hormone; SST, somatostatin; TRH, thyroxine-releasing hormone; CRH, corticosteroid-releasing hormone; TSH, thyroxine-stimulating hormone; ACTH, adrenocorticotropic hormone; IGF1, insulin-like growth factor 1; SRD5A1, 5 α -reductase 1; HSD11B1, 11 β -hydroxysteroid dehydrogenase 1.

pituitary, respectively (Wagner *et al.* 1998, Low *et al.* 2001). Sex differences in the number of GHRH and SST neurons that appear during adulthood are responsible for sex differences in GH secretion patterns, with adult males having more frequent higher amplitude secretory pulses than adult females (Tannenbaum & Martin 1976, Edén 1979).

During the early postnatal period, sex differences in GH release are not yet apparent but testosterone exposure on the first day of life will determine the sex-specific pattern of GH release in adulthood (Murray *et al.* 1999, Chowen *et al.* 2004). For example, prevention of the neonatal testosterone surge by gonadectomy on the day of birth feminizes the GH secretory pattern by reducing GHRH and SST mRNA levels as well as the number of hypothalamic GHRH neurons (Chowen *et al.* 1996). Similarly, neonatal testosterone exposure masculinizes GH release in the female rat by increasing hypothalamic SST mRNA (Chowen *et al.* 1996). Importantly, the organizational influence of testosterone only occurs after its local conversion to estradiol by aromatase in the brain, as evidenced by the masculinizing effect of exogenous estradiol and the lack of effect by the non-aromatizable androgen dihydrotestosterone (Simonian *et al.* 1998). The neonatal testosterone surge therefore establishes the sexual dimorphism of hypothalamic and pituitary mediators of GH pulsatility that emerge as testicular testosterone production resumes at puberty. This results in sex-specific patterns of GH pulsatility that affect hepatic gene expression differently during the period of pubertal to adult transition, as described below.

Early postnatal HPA 'hyporesponsivity' reflects low CBG levels

The first 2 postnatal weeks have been termed the 'stress hyporesponsive period' because of an apparent inability of the rat neonate to show adult-like elevations in corticosterone in response to stress (Sapolsky & Meaney 1986). While the adrenal gland is hyporesponsive to ACTH stimulation during this time (Yoshimura *et al.* 2003), the rest of the HPA axis is functionally intact, for example, changes occur in the expression of CRH mRNA, plasma ACTH and corticosterone in response to stress (Dallman 2000, Dent *et al.* 2000). Furthermore, the degree of HPA axis activation as assessed by GR occupancy and nuclear translocation in the brain is comparable in rats of all ages, including the neonate (Viau *et al.* 1996). It is now understood that the small increases in plasma corticosterone in the neonate reflect the limited hepatic

expression of *SerpinA6* and the very low plasma CBG levels at this time (Henning 1978, D'Agostino & Henning 1981, Smith & Hammond 1991, Viau *et al.* 1996), as less adrenal corticosterone output is required at this stage to maintain free corticosterone levels. This activity of the HPA axis is also reflected in the low expression level of *Hsd11b1* and *Srd5a1*, which steadily increase in expression from birth to adulthood (Hundertmark *et al.* 1994, Yu *et al.* 2014). Thus, the HPA axis is active during PDs 1–15 although its components are lower in number and concentration.

Postnatal maturation of the HPT axis

The liver produces another important plasma hormone carrier, thyroxine binding globulin (TBG), which binds the majority of thyroxine (T4) in the circulation (75% in humans) with high affinity (Savu *et al.* 1987, Vranckx *et al.* 1990b). Plasma TBG plays an important role in controlling the HPT axis, a neuroendocrine network that undergoes rapid maturation after birth to promote the development of many organ systems (Zoeller *et al.* 2007). Like CBG, TBG is a SERPIN family member with gene name *SerpinA7*, and is exclusively expressed in the rat liver between postnatal days (PDs) 3–45, peaking at day 15 and declining thereafter to low levels until senescence (Vranckx *et al.* 1990a, Savu *et al.* 1991). A similar developmental pattern is observed in humans (Refetoff 2000), although TBG levels are still relatively high in adulthood (180–350 nM) whereas in adult rats they are less than 15 nM (Emerson *et al.* 1993). This change in hepatic TBG production with respect to age suggests that it plays an important role in the maturation of the HPT axis.

Within the HPT axis, thyrotropin-releasing hormone (TRH) is released from the hypothalamus in response to low circulating thyroid hormone levels, promoting thyroid-stimulating hormone (TSH) secretion by thyrotrophs in the anterior pituitary (Ortiga-Carvalho *et al.* 2016). Notably, hypothalamic TRH neurons are located in proximity to CRH neurons and are also glucocorticoid-sensitive, suggesting that these systems interact at the hypothalamic level (Cintra *et al.* 1990). Circulating TSH acts on the thyroid to produce predominantly T4, which is converted to its active form triiodothyronine (T3) in peripheral tissue, and the access of thyroid hormones to their target tissues is influenced by TBG. Other liver-expressed plasma proteins, transthyretin and albumin, also bind thyroid hormones in the human and rodent (15 and 10% of human plasma T4, respectively) but with much lower affinity than TBG (Rabah *et al.* 2019) and

they do not appear to be required for thyroid hormone homeostasis in humans (Woeber & Ingbar 1968).

Significant increases in plasma TBG concentrations during the first 2 postnatal weeks in rats facilitate increases in total and free T4 (Dussault & Labrie 1975, Walker *et al.* 1980) that are critical for the developing brain and other organ systems. From this perspective, the liver controls the maturation of the HPT axis through modulation of plasma TBG production. Importantly, thyroid hormones represent one of the major endocrine regulators of hepatic *SerpinA6* expression and plasma CBG levels, and sub-threshold thyroid hormone levels during this time may in part explain the low plasma CBG levels and HPA axis 'hyporesponsivity' from PDs 1 to 15 in the rat (Dussault & Labrie 1975), revealing how the liver uses cues from the HPT axis to initiate HPA axis development (Fig. 1).

Juvenile period (postnatal days 15–30): HPA activation by thyroid hormone

During the juvenile period in rats, gonadal testosterone production is quiescent (Bell 2018), while high thyroid hormone levels promote the up-regulation of CBG production in the liver required to mature the HPA axis (Fig. 2).

Thyroid hormones stimulate hepatic CBG production and HPA axis development

A critical threshold of plasma T4 established around PD 15 may explain the observed decline in plasma TBG at this time, since TBG is negatively regulated by thyroid hormones in adult rats (Savu *et al.* 1992). This threshold may also be achieved due to increased expression of

Figure 2

The juvenile period: HPA activation by thyroid hormone. Three endocrine axes that interact with the liver are highlighted by color: SST-GH-T (green), HPT (orange), and HPA (purple). Charts depict plasma levels of key components with respect to postnatal age in males (solid line) and females (dashed line). During postnatal days 15–30, plasma TBG levels decline while total and free T4 remain high, driving hepatic CBG production. Increases in plasma CBG levels facilitate increased CORT production and adrenal growth. In this way, the HPA axis is activated and matures in both sexes. HPT, hypothalamic-pituitary-thyroid; HPA, hypothalamic-pituitary-adrenal; PD, postnatal day; GH, growth hormone; TBG, thyroxine-binding globulin; T4, thyroxine; T, testosterone; CBG, corticosteroid-binding globulin; CORT, corticosterone; GHRH, growth hormone releasing hormone; SST, somatostatin; TRH, thyroxine-releasing hormone; CRH, corticosteroid-releasing hormone; TSH, thyroxine-stimulating hormone; ACTH, adrenocorticotropic hormone; IGF1, insulin-like growth factor 1; SRD5A1, 5 α -reductase 1; HSD11B1, 11 β -hydroxysteroid dehydrogenase 1.

iodothyronine deiodinase type 1, the primary hepatic enzyme that facilitates the conversion of T4 to T3, since the transcript levels of this enzyme reach adult levels between PD 10 and 20 in rats (Bates *et al.* 1999).

High total and free T4 levels around PD 15 are thought to induce hepatic *Serpina6* expression, as evidenced by thyroid hormone-induced increases in plasma CBG levels in juvenile rats (D'Agostino & Henning 1982b) and hepatic CBG mRNA and plasma levels in adult male rats (Smith & Hammond 1991). Furthermore, TSH is the only anterior pituitary hormone that rescues low CBG levels in hypophysectomized adult female rats, demonstrating that CBG levels are modulated by the activity of the HPT axis (Gala & Westphal 1966b). Rising corticosterone levels during PDs ~15–30 may further suppress hepatic TBG production, since TBG is negatively regulated by corticosterone, as shown by adrenalectomized male and female rats that have high TBG levels which normalize after corticosterone replacement (Emerson *et al.* 1993).

The requirement for proper thyroid function in HPA axis development in rodents is further supported by reports that hypothyroid male rats have lower adrenal weight and plasma corticosterone, and higher ACTH, CRH, and arginine vasopressin (Kamilaris *et al.* 1991, Tohei 2004). Similarly, hyperthyroidism results in increased plasma corticosterone, CBG, ACTH, POMC mRNA, adrenal sensitivity to ACTH, and accelerated maturation of hypothalamic CRH expression in rats (Kamilaris *et al.* 1991). Increases in plasma CBG levels drive maturation of the HPA axis during the juvenile period because it introduces demand on the adrenal gland to maintain free corticosterone levels. As a result, adrenal *zona fasciculata* size and total corticosterone levels increase in parallel with CBG (Gala & Westphal 1965, Pignatelli *et al.* 2006). Taken together, increases in thyroid hormone levels facilitated by hepatic TBG production are sensed by the liver, resulting in increased plasma levels of CBG, that in turn modulate the total and free glucocorticoid hormone levels in the circulation that act to promote the activation and maturation of HPA axis (Fig. 2).

Pubertal to adult transition (postnatal days 30–60): sexual dimorphism of the HPA axis

At the pubertal to adult transition, the production and metabolism of glucocorticoids become sexually dimorphic in rodents, resulting in much higher total corticosterone levels in females (Fig. 3). This can be largely attributed to the advent of sexually dimorphic patterns of plasma

GH pulsatility as programmed by neonatal testosterone and its differential impact on the production of IGF1, CBG and key glucocorticoid-metabolizing enzymes by the rat liver. Conversely, sex differences within the HPT axis remain minimal in adulthood (Waner & Nyska 1988, Emerson *et al.* 1993) and therefore have little influence on the sexual dimorphism of the HPA axis.

Growth hormone pulsatility and its sex-specific effects on CBG levels

The emergence of sex differences in the pituitary release of GH around PD 33 (Gabriel *et al.* 1992) plays a major role in establishing sexual dimorphism of the HPA axis and other systems. The sex-specific pattern of GH release in the adult rat is organized by testosterone exposure in early neonatal life, and is triggered by the re-initiation of testicular testosterone production in males at puberty (Jansson *et al.* 1985a, Chowen *et al.* 1993, Viau 2002, Goel *et al.* 2014a). At ~PD 30 when testosterone and body weight begin to increase to a greater level in males, they begin to exhibit pulsatility in GH secretion by producing peaks of ~200 ng/mL plasma GH every ~3.5 h that are followed by 2-h intervals with no GH (Tannenbaum & Martin 1976). In contrast, females maintain continuous release of GH to establish steady plasma concentrations of ~30–60 ng/mL (Edén 1979). It is therefore thought that the default organization of the SST-GH axis is feminine (Adams *et al.* 2015), since testosterone input is required to obtain a masculine phenotype.

Importantly, variations in GH pulsatility can account for sex differences in plasma CBG levels and HPA axis activity in rats. Continuous infusion of GH to resemble a feminine pattern of GH secretion increases plasma CBG in hypophysectomized male and female rats, while intermittent GH replacement in females to resemble a masculine pattern of GH release either has no effect or suppresses CBG levels (Jansson *et al.* 1989). It has been reported that SST-deficient mice are feminized, since GH is released in a continuous manner, plasma CBG and corticosterone levels are increased, and the sex difference in adrenal weight is lost (Adams *et al.* 2015). Furthermore, hypophysectomy and gonadectomy in adult female rats reduce plasma CBG levels whereas hypophysectomy in the male increases plasma CBG, and these effects were seen despite replacement therapy with thyroxine, glucocorticoids, androgen or estrogen (Jansson *et al.* 1989), suggesting that growth hormone maintains the sexually dimorphic CBG levels. Thus, the sex difference in plasma CBG levels appears to emerge as a consequence

Figure 3

Pubertal to adult transition: sexual dimorphism of the HPA axis. (A) Male. (B) Female. Three endocrine axes that interact with the liver are highlighted by color: SST-GH-T (green), HPT (orange), and HPA (purple). Charts depict plasma levels of key components with respect to postnatal age in males (solid line) and females (dashed line). After postnatal day 30, testosterone levels in the male increase while female levels remain low. Testosterone stimulates the neonatally programmed SST and GHRH neurons to induce a pulsatile release of GH from the anterior pituitary of the male, while the female maintains continuous release. Sexually dimorphic GH patterns are sensed by the liver, causing sex differences in the abundances of IGF1, CBG, HSD11B1 and SRD5A1. Higher plasma CBG in females causes greater plasma CORT levels and adrenal size compared to the male. Sex differences in the activities of hepatic HSD11B1 and SRD5A1 influence circulating CORT levels, further driving sexual dimorphism throughout the HPA axis. HPT, hypothalamic-pituitary-thyroid; HPA, hypothalamic-pituitary-adrenal; PD, postnatal day; GH, growth hormone; TBG, thyroxine-binding globulin; T4, thyroxine; T, testosterone; CBG, corticosteroid-binding globulin; CORT, corticosterone; GHRH, growth hormone releasing hormone; SST, somatostatin; TRH, thyroxine-releasing hormone; CRH, corticosteroid-releasing hormone; TSH, thyroxine-stimulating hormone; ACTH, adrenocorticotrophic hormone; IGF1, insulin-like growth factor 1; SRD5A1, 5 α -reductase 1; HSD11B1, 11 β -hydroxysteroid dehydrogenase 1.

of sexual dimorphism in pituitary GH pulsatility around PD 30 in rats.

Mediation of growth hormone action by IGF1

Experimental evidence suggests that growth hormone mediates its effects on hepatic CBG expression through the actions of IGF1. In the GH-IGF axis, growth hormone directly stimulates hepatic *Igf1* expression and IGF1 suppresses pituitary GH release in a negative feedback manner (Jones & Clemmons 1995). Hepatic IGF1 mRNA levels increase steadily in the rat until PD 30, when male levels increase markedly in response to the establishment of a pattern of plasma GH pulsatility (Shoba *et al.* 1999) that departs from IGF1 levels in females (Frystyk *et al.* 1998). *In vitro*, IGF1 negatively regulates hepatic *SERPINA6* expression (Crave *et al.* 1995), providing a potential mechanism by which variations in GH pulsatility and subsequently IGF1 affect CBG levels. Interestingly, IGF1 is sensitive to ovarian status, since its mRNA and protein levels are downregulated by estrogen and upregulated by testosterone in ovariectomized rats (Borski *et al.* 1996), further implicating IGF1 in the development and/or maintenance of sexually dimorphic systems.

HPA axis sexual dimorphism is programmed by neonatal testosterone

Manipulation of sex steroid hormones during critical perinatal periods can masculinize or feminize the HPA axis. Male rats treated with the antiandrogen flutamide from gestational day 13 to PD 20 show changes in the corticosterone secretion pattern and brain HPA markers that reflect feminization (Seale *et al.* 2005). Adult CBG levels are also influenced by neonatal androgen exposure: male rats castrated at birth develop feminized plasma CBG levels in adulthood, and animals of both sexes gonadectomized at birth and treated with testosterone propionate have very low CBG levels in adulthood (Van Baelen *et al.* 1977, Jansson *et al.* 1989). Interestingly, gonadectomy on day 25 also increased CBG levels in males although to a lesser extent than when performed at birth, and testosterone replacement reversed these effects (Jansson *et al.* 1989), demonstrating that both the organizational effects of neonatal testosterone and the activational effects of pre-pubertal testosterone are required to establish sexual dimorphism of the HPA axis. Furthermore, testosterone in adulthood is known to suppress CBG and HPA axis activity in females, whereas estradiol is stimulatory in males (Gala & Westphal 1966a,

Viau 2002, Viau & Meaney 2004, McCormick & Mathews 2010, Goel *et al.* 2014a). The contribution of chromosomal sex vs gonadal hormones to the sexual dimorphism of the HPA axis remains unknown. However, some studies have utilized the four core genotypes mouse model to show that sex differences in the morphology of arginine vasopressin fibres in the lateral septum – a region known to influence the HPA axis – is caused by both chromosomal sex and gonadal hormone exposure (Gatewood *et al.* 2006, Arnold & Chen 2009). The organizational influences of gonadal steroids on the HPA axis may be mediated by GH pulsatility, to explain lower plasma CBG levels, reduced adrenal size and lower corticosterone concentrations in males than in females (Gala & Westphal 1965, Henning 1978, Smith & Hammond 1991, Pignatelli *et al.* 2006). However, this remains to be seen since GH pulsatility patterns were not measured in studies relating neonatal testosterone exposure to adult HPA axis function.

Plasma ACTH has trophic effects on the adrenal gland, but plasma ACTH levels are not sexually dimorphic in adult rats and therefore cannot explain sex differences in adrenal gland size (Goel *et al.* 2014b). This has led to the hypothesis that sex differences in adrenal size emerge due to differences in adrenal sensitivity to ACTH (Goel *et al.* 2014b). However, the actions of CBG at the adrenal gland may also play a key role in determining adrenal size, since evidence suggests corticosterone represses steroidogenesis in the adrenal itself (Spiga *et al.* 2017). It may therefore be envisaged that CBG acts to reduce intra-adrenal negative feedback, especially in females where the higher plasma CBG levels accentuate the local release and removal of corticosterone from the adrenal cells, thereby promoting adrenal cortical expression of transcription factors such as SF-1 and DAX-1 that regulate both steroidogenesis and adrenal growth (Spiga *et al.* 2017).

GH-sensitive hepatic steroid-metabolizing enzymes maintain HPA sexual dimorphism

Growth hormone induces sex differences in HPA axis tone by affecting plasma CBG levels, but also by changing the expression of hepatic glucocorticoid-metabolizing enzymes that contribute to the regulation of plasma glucocorticoid levels: HSD11B1 and SRD5A1 (Fig. 3).

11 β -hydroxysteroid dehydrogenase 1 (HSD11B1)

The enzyme HSD11B1 regenerates active glucocorticoid by converting inert cortisone or 11-dehydrocorticosterone to active cortisol and corticosterone, respectively. It is most abundant in the liver but can be found in many tissues

throughout the body including adipose, hippocampus, hypothalamus and pituitary (Chapman *et al.* 2013). Since HSD11B1 acts to amplify local glucocorticoid concentrations independent of circulating concentrations, its action in these tissues leads to increased local glucocorticoid signaling, influencing negative feedback in the brain and metabolic actions in the liver (Harris *et al.* 2001). Hepatic HSD11B1 contributes to 20–40% of daily cortisol production in humans and elevations in its activity are thought to up-regulate the glucocorticoid-sensitive processes of gluconeogenesis and fatty acid oxidation (Masuzaki & Flier 2003, Basu *et al.* 2004, Walker & Andrew 2006, Maniam *et al.* 2014).

The isozyme HSD11B2 performs the reverse reaction that inactivates glucocorticoid. Its major functions are in the kidney where it ensures aldosterone is the prevailing substrate of the MR, and in the placenta where it protects the fetus from excessive glucocorticoid exposure. The actions of HSD11B2 during early life can influence the programming of the HPA axis: adult offspring of rats treated with an HSD11B inhibitor show increased basal glucocorticoid levels, increased CRH and reduced GR mRNA in the hypothalamic paraventricular nucleus (Welberg *et al.* 2000), and *Hsd11b2*^{-/-} mice have smaller adrenal glands and heightened anxiety (Holmes *et al.* 2006). The activities of HSD11B2 would alter substrate availability for HSD11B1 in tissues where it is expressed, but its hepatic expression is minimal in humans, rats and mice (Chapman *et al.* 2013, Yu *et al.* 2014), suggesting HSD11B2 is unlikely to influence circulating glucocorticoid levels. Thus, hepatic HSD11B1 is the crucial determinant of intracellular and circulating glucocorticoid availability, and the developmental regulation of its production in the liver is determined by the same endocrine systems that control other major components of the HPA axis (Maniam *et al.* 2014), as will be discussed.

Direct manipulation of *Hsd11b1* expression *in vivo* has mostly been performed in male mice. All strains of mice lacking HSD11B1 have larger adrenals and exaggerated corticosterone responses to stress compared to their WT littermates, and this change in adrenal size is thought to occur as compensation to replace glucocorticoid that is normally regenerated by hepatic HSD11B1. Basal corticosterone levels are either unchanged (Lavery *et al.* 2012, Morgan *et al.* 2014, Yau *et al.* 2015) or increased (Kotelevtsev *et al.* 1997, Harris *et al.* 2001) in HSD11B1-deficient mice, and these contrasting observations may reflect strain differences: C57Bl/6 mice show increases in GR mRNA at negative feedback sites and a lesser degree of adrenal hypertrophy compared to 129/MF1 mice, which may explain and/or

reflect the unchanged corticosterone levels (Carter *et al.* 2009). Interestingly, C57Bl/6 mice overexpressing *Hsd11b1* in the liver crossed with global *Hsd11b1*-deficient mice to selectively restore hepatic HSD11B1 production rescues all of the HPA axis defects, including circadian and stress-induced plasma corticosterone levels (Paterson *et al.* 2007). These data implicate hepatic HSD11B1 as a key player in HPA axis regulation and suggests that it contributes to the development and sexually dimorphic activity of the HPA axis in rats as well.

Several hepatic glucocorticoid-metabolizing enzymes are sexually dimorphic and programmed by neonatal sex steroids (Einarsson *et al.* 1973). Hepatic *Hsd11b1* expression increases near parturition in rats and progressively with advancing postnatal age (Hundertmark *et al.* 1994), becoming sexually dimorphic as sex differences in GH pulsatility are achieved (Low *et al.* 1994). The feminine GH pattern of continuous pituitary release results in 50% lower HSD11B1 mRNA and activity in the female liver compared to male (Low *et al.* 1994, Ahluwalia *et al.* 2004), and this is thought to be mediated by IGF1 (Chapman *et al.* 2013). Greater intracellular glucocorticoid levels in the male may explain reduced CBG levels since glucocorticoids directly suppress CBG production (Feldman *et al.* 1979, Schlechte & Hamilton 1987). Thus, sexual dimorphism in hepatic HSD11B1 activity provides an explanation for sex differences in hepatic and plasma corticosterone levels, as well as the negative feedback regulation of CBG production.

Dwarf rats congenitally deficient in GH lack sex differences in HSD11B1 activity, and administration of continuous GH to males decreases hepatic HSD11B1 activity and gene expression. Similarly, continuous GH administration to hypophysectomized dwarf rats attenuates hepatic HSD11B1 activity and gene expression (Low *et al.* 1994). Sex steroids may also regulate HSD11B1, since testosterone administration to gonadectomized rats of either sex induces masculine activity levels (Lax *et al.* 1978), and estradiol at pharmacological doses represses hepatic *Hsd11b1* expression and activity (Jamieson *et al.* 1999). Last, thyroid hormone has sex-specific effects since its administration reduces hepatic HSD11B1 activity in males but increases its activity in females (Liu *et al.* 1997). Regulation of hepatic *Hsd11b1* expression by the same endocrine factors which control other HPA axis components implicate HSD11B1 as a key player in the age-, sex- and context-specific actions of the HPA axis.

5 α -reductase 1 (SRD5A1)

Glucocorticoids are irreversibly inactivated by 5 α -reductase in the liver, and SRD5A1 is involved in the control of

cellular and circulating glucocorticoid levels and therefore has implications in the development and function of the HPA axis (Nixon *et al.* 2012, Crowley *et al.* 2014). The SRD5A1 enzyme is expressed highly in human and rodent livers and at lower levels in the adrenal and brain, including within afferent mediators to the HPA axis and sites of glucocorticoid negative feedback (Nixon *et al.* 2012). Its major substrates are cortisol, corticosterone, testosterone and progesterone and their catabolism by SRD5A1 in the liver plays an important role in their plasma clearance (Nixon *et al.* 2012), as illustrated in SRD5A1-deficient mice that have an eight-fold slower clearance of corticosterone (Livingstone *et al.* 2014) and display intrahepatic accumulations of glucocorticoids (Dowman *et al.* 2013). In these SRD5A1-deficient mice, resting plasma corticosterone levels and adrenal weight are normal and chronic infusion of corticosterone does not alter plasma corticosterone levels compared to WT mice. However, the corticosterone response to ACTH and stress is notably reduced, suggesting that enhanced negative feedback by corticosterone resulting from its impaired peripheral clearance causes a compensatory downregulation of the HPA axis in SRD5A1 deficiency. The effects of SRD5A1 deficiency may manifest differently across strains and species given that only the C57Bl6/SvEv/129 mouse background has been investigated. Notably, the phenotype of SRD5A1-deficient mice is similar to that seen in HSD11B1-deficient mice on the same 129/MF1 background (Livingstone *et al.* 2014). In addition to the tissues mentioned above, human *SRD5A1* is expressed in numerous others including adipose, kidney, intestine, lymph nodes and thyroid (Fagerberg *et al.* 2014), expanding the sites of glucocorticoid metabolism that will likely influence HPA tone differently compared to the rat.

Hepatic expression of *Srd5a1* is sexually dimorphic in the rat, with approximately 20-fold higher mRNA and activity in females (Andersson *et al.* 1989). In males, testosterone negatively regulates SRD5A1, since gonadectomy of neonatal and pre-pubertal male rats increases hepatic SRD5A1 transcripts or activity (Jansson *et al.* 1985b), and gonadectomy of sexually mature male rats also increases SRD5A1 mRNA (El-Awady *et al.* 2004), explaining their low expression levels compared to the female. In females, the regulation of hepatic SRD5A1 by testosterone is less clear since adult females treated with testosterone have even higher SRD5A1 levels than normal, and adult ovariectomy also increases *Srd5a1* mRNA (Torres & Ortega 2004). However, when females are masculinized by neonatal

gonadectomy followed by testosterone treatment in adulthood, hepatic SRD5A1 levels are reduced, revealing the organizational effects of testosterone on the regulation of *Srd5a1* (Jansson *et al.* 1985b). These observations also implicate GH pulsatility in determining SRD5A1 levels, since GH release patterns were masculinized by these manipulations (Jansson *et al.* 1985b). Indeed, continuous infusion of GH increases hepatic SRD5A1 activity in hypophysectomized, hypothyroid males, and to a greater extent than in hypophysectomized, euthyroid males (Jansson *et al.* 1985b), demonstrating the influences of both GH pulsatility and thyroid hormone on SRD5A1. The sensitivity of corticosterone metabolism to thyroid hormone, GH, and sex steroids predict that changes in hepatic *Srd5a1* expression may also contribute to the development and sexual dimorphism of the HPA axis.

Conclusions

Organ development is an energetically demanding process that relies on cues to trigger progression, and the liver provides many of these cues concurrently with its fundamental role in maintaining metabolic homeostasis. This review introduces a framework for understanding the mechanisms behind the postnatal ontogeny and sexual dimorphism of the HPA axis in rats, advancing the concept that the liver is an important mediator of these processes. Specifically, the liver integrates endocrine signals from the SST-GH-testosterone, HPT, and HPA axes to modulate the expression of the major plasma binding proteins for thyroid hormone and glucocorticoids, TBG and CBG, respectively, as well as hepatic glucocorticoid- and thyroid hormone-metabolizing enzymes HSD11B1, SRD5A1 and iodothyronine deiodinases that in turn regulate these same endocrine regulatory axes to promote their maturation. Developmental changes in the activities of these endocrine systems as coordinated by the liver are key to age-, sex- and context-dependent physiological responses critical for homeostatic control, which is essential for survival and propagation of species.

Comparisons to humans

Rats are a preferred model of human disease because their physiology, cognitive abilities and behavioral responses better resemble the human, compared to mice (Iannaccone & Jacob 2009). Many of the endocrine interactions reviewed here with respect to postnatal HPA axis development are conserved in humans, though

the literature in humans is less consistent due to the diversity of demography, age and health status, time and source of sampling, and the type of stimulus (Goel *et al.* 2014b). Both human and rat acquire sex differences in HPA activity during puberty (Kudielka *et al.* 2004, Goel *et al.* 2014b) and this can be explained by the activities of sex hormones; fetal testosterone levels correlate with neurodevelopmental disease risk and behavioral stress reactivity (Gore *et al.* 2014), and certain stress-related disorders such as depression and anxiety are more prevalent in women (Albert 2015). In humans, the sex difference in GH secretion is less pronounced compared to the rat, and also reversed, such that females secrete more GH due to more pulses (Hartman *et al.* 1990). Despite this, adults with GH deficiency show an effect of GH replacement to decrease plasma IGF1, CBG and cortisol, with no change in thyroid hormone or thyroxine-binding globulin levels (Tschöp *et al.* 2000); interactions that are consistent with the rat. Human GH may have the opposite effect on hepatic HSD11B1, however, since urinary cortisol metabolite profiles suggest GH is inhibitory (Moore *et al.* 1999), whereas rat GH is stimulatory to HSD11B1 activity (Low *et al.* 1994, Ahluwalia *et al.* 2004). Regulation of plasma glucocorticoid concentrations is critical to hepatic and HPA function in humans as in the rat, shown by the prevalence of adrenal insufficiency in cases of liver cirrhosis (McNeilly *et al.* 2010, Livingstone *et al.* 2014) and in the development of hepatic insulin resistance and intrahepatic lipid accumulation during SRD5A1 deficiency (Hazlehurst *et al.* 2016). Notably, human CBG levels are only sexually dimorphic in response to oral contraceptives (Verbeeten & Ahmet 2018), during pregnancy (Meyer *et al.* 2016) and aging (Kudielka *et al.* 2004), which may in part explain the less overt sex differences of the human HPA axis compared to the rat.

Many of the molecular relationships reviewed here have been studied independently, and functional linkages between these factors of interest remain worthy of pursuit. Other regulators of metabolic homeostasis such as the CNS and immune system are, in addition to the liver, critical for HPA function, and their actions have yet to be considered in the context of postnatal HPA axis development and its sexual dimorphism. Importantly, knowledge of the interplay between the liver, HPT, and HPA axes in postnatal rats can advance our understanding of pathophysiologies related to the HPA axis in humans, and sex differences in the rodent HPA axis offer a useful model of interindividual and sex differences in the development and function of the human HPA axis.

Declaration of interest

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

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