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STUDENT AWARDEE PAPER

Minireview: Glucocorticoid–Leptin Crosstalk: Role of Glucocorticoid–Leptin Counterregulation in Metabolic Homeostasis and Normal Development

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Synopsis Glucocorticoids and leptin are two important hormones that regulate metabolic homeostasis by controlling appetite and energy expenditure in adult mammals. Also, glucocorticoids and leptin strongly counterregulate each other, such that chronic stress-induced glucocorticoids upregulate the production of leptin and leptin suppresses glucocorticoid production directly via action on endocrine organs and indirectly via action on food intake. Altered glucocorticoid or leptin levels during development can impair organ development and increase the risk of chronic diseases in adults, but there are limited studies depicting the significance of glucocorticoid-leptin interaction during development and its impact on developmental programming. In mammals, leptin-induced suppression of glucocorticoid production is critical during development, where leptin prevents stress-induced glucocorticoid production by inducing a period of short-hyporesponsiveness when the adrenal glands fail to respond to certain mild to moderate stressors. Conversely, reduced or absent leptin signaling increases glucocorticoid levels beyond what is appropriate for normal organogenesis. The counterregulatory interactions between leptin and glucocorticoids suggest the potential significant involvement of leptin in disorders that occur from stress during development.

Abbreviations

GCs	glucocorticoids
GR	glucocorticoid receptor
CRF	corticotropin releasing factor
ACTH	adrenocorticotropic hormone
TH	thyroid hormone
SHRP	short-hyporesponsiveness
POMC	proopiomelanocortin
CART	cocaine- and amphetamine-regulated transcript
NPY	neuropeptide Y
agrp	agouti-related protein
mc2r	melanocortin type 2 receptor
star	cholesterol transporter
cyp21a2	21-hydroxylase
P450SCC	side-chain cleavage enzyme
PBR	peripheral-type benzodiazepine receptor
ARC	arcuate nucleus
PVN	paraventricular nucleus
VMN	ventromedial nucleus
HPA	hypothalamic pituitary adrenal

1. Introduction

Glucocorticoids (GCs) and leptin are two hormones that have well-established roles in appetite regulation, metabolism, growth, reproduction, immune function, and organogenesis (Ahima et al. 2000; Coutinho and Chapman 2011; Chan et al. 2014; Procaccini et al. 2017; Whirledge and Cidlowski 2017; Swarbrick et al. 2021). GCs are steroid hormones whose production from adrenal glands is stimulated by corticotropin-releasing factor (CRF) produced by the paraventricular nucleus of the hypothalamus, followed by adrenocorticotropic hormone (ACTH) produced by the anterior pituitary (Vale et al. 1981; Antoni 1986; Tonon et al. 1986; Laugero et al. 2002; Kühn et al. 2004; Kühn et al. 2005; Mccormick and Bradshaw 2006; Prunet et al. 2006; Bury and Sturm 2007; Denver 2009). GCs regulate their own production through negative feedback to the hypothalamic pituitary adrenal (HPA) axis, by downregulating the production of CRF and ACTH in the brain, and certain steroidogenic enzymes in the

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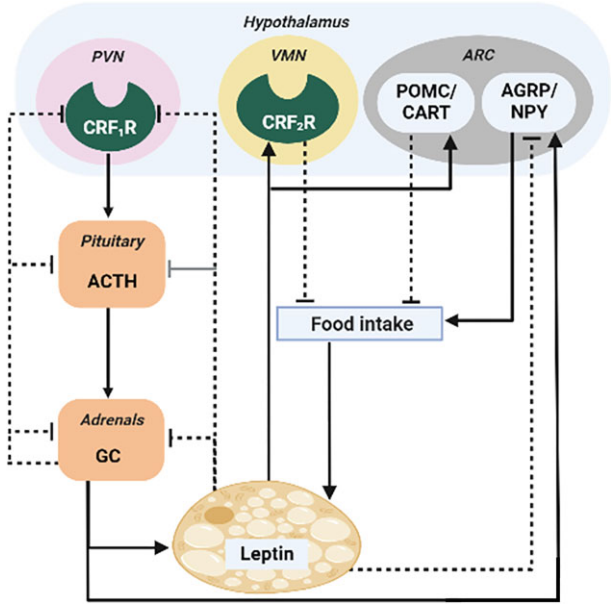

Fig. 1 Counterregulatory interaction between GCs and leptin in regulating hormone levels and food intake. Solid black lines: stimulatory effect; dashed black lines: inhibitory effect; solid gray line: apparent/hypothesized inhibitory effect (lacks adequate evidence); PVN: paraventricular nucleus; VMN: ventromedial nucleus; ARC: arcuate nucleus; AGRP: agouti-related protein; NPY: neuropeptide Y; POMC: proopiomelanocortin; CART: cocaine- and amphetamine-regulated transcript; CRF: corticotropin-releasing factor; ACTH: adrenocorticotropic hormone; GC: glucocorticoid; CRF_1R: CRF receptor 1; and CRF_2R: CRF receptor 2.

adrenals (Gesina et al. 2004; Forhead and Fowden 2009; De Guia et al. 2014; Nicolaides et al. 2014; Paul et al. 2022). This negative feedback loop is crucial to maintain baseline GC levels to protect the body from the harmful effects of GC overexposure (Fig. 1). Leptin is a cytokine hormone secreted mainly by adipose tissue regulating appetite and energy balance (Tartaglia et al. 1995; Heiman et al. 1997; Clément et al. 1998; Dallongeville et al. 1998). Circulating leptin suppresses appetite directly by increasing the activity of anorexigenic proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons, and indirectly by decreasing the activity of the orexigenic agouti-related protein (AGRP) and neuropeptide Y (NPY) neurons in the arcuate nucleus of the hypothalamus (Fig. 1; Ostlund et al. 1996; Elias et al. 1998; Minocci et al. 2000; Cowley et al. 2001; Flak and Myers 2016). Also, through a negative feedback loop, leptin downregulates its own production directly by reducing leptin mRNA and indirectly through the breakdown of adipose tissue deposits releasing fatty acids and glycerol (Frühbeck et al. 1997; Wang et al. 1999). Apart from the adipose tissue, leptin is produced in small quantities by the brain, placenta, skeletal muscles, mammary gland, bone marrow, and stomach (Obradovic et al. 2021). In addition to independently regulating appetite and metabolism, for more than two decades we have known that leptin and GCs counterregulate each other to fine-tune energy intake and expenditure in adults (Bornstein et al. 1997; De Vos et al. 1998; Solano and Jacobson 1999; Askari et al. 2000; Nye et al. 2000).

Fetal development is associated with dramatic morphological and physiological changes coordinated by a network of autocrine, paracrine, and endocrine factors and the hormones with well-established roles in fetal development include GCs, thyroid hormone, and insulin. For example, GCs are necessary for efficient maturation of multiple organs, mainly lungs, brain, heart, liver, and kidneys (Turkay et al. 2012). Lack of GC signaling in tissue-specific or constitutive glucocorticoid receptor (GR) knockout mammals results in a range of debilitating phenotypes such as death at birth, abnormal growth and development, and adult disease phenotypes (Wyrwoll and Holmes 2012; Whirledge and Defranco 2018). Leptin is among the hormones with less recognized roles in development. Our current understanding about the significance of leptin during fetal development mostly stems from rodent models, which have reported expression of leptin receptor and leptin synthesis in the placenta and several fetal organs like brain, heart, bone, cartilage, lung, liver, and kidney (Dallongeville et al. 1998; Górska et al. 2009; Haggard et al. 1998). Leptin antagonism can adversely affect the maturation of kidney, pancreas, brain, lungs, and ovary (Steppan and Swick 1999; Huang et al. 2008; Attig et al. 2011; Briffa et al. 2015; De Blasio et al. 2016). However, the lack of experimental investigations based on primate and human models obscures our understanding of the absolute necessity of leptin for human organogenesis and the development of therapeutics targeting disorders arising from abnormal leptin signaling. Apart from their independent role in modulating fetal development, GCs and leptin frequently interact with each other to efficiently regulate organogenesis. (Bernstein et al. 1983; De Groef et al. 2013; Sachs and Buchholz 2019). For example, decrease in leptin levels during development results in excessive GC production, which can cause irreversible damage to neonatal organs (Tegethoff et al. 2009; Rog-Zielinska et al. 2013; Malaeb and Stonestreet 2014). Importantly, it is not clearly known whether the phenotypic effects of abnormal leptin or GC signaling during development is due to one hormone alone or include altered amounts of signaling by the other hormone as well.

In this minireview, we summarize our current knowledge about the mechanisms of GC–leptin counterregulation and the potential necessity of such interaction for maintenance of adult metabolic homeostasis and for normal development in vertebrates. We will further

discuss how interpretations of the individual developmental effects of GCs and leptin should be expanded in light of the interactions between GCs and leptin.

2. GC-induced leptin upregulation and leptin-induced suppression of GC production

GCs can elevate leptin levels directly by increasing the transcription of leptin mRNA. GCs directly induce leptin production via a GC response element in the promoter region of the human leptin gene (De Vos et al. 1998). GC-mediated direct increase in leptin mRNA is observed *in vitro* in rat adipose tissue (Masuzaki et al. 1997). GC treatment increases leptin protein synthesis *in vitro* in adipose tissue from pregnant and nonpregnant mice and cultured human adipocytes and elevates plasma leptin levels *in vivo* in humans and rats (Wabitsch et al. 1996; Masuzaki et al. 1997). GC action on leptin requires glucocorticoid receptor because (1) siRNA-mediated silencing of glucocorticoid receptor in human adipocytes inhibited GC-induced leptin mRNA and protein production (Rhodes and Yamada 1995; Leal-Cerro et al. 2001; Lee et al. 2014; Madison et al. 2015), and (2) dexamethasone (a GR agonist) increased leptin mRNA levels in rat adipocytes (Murakami et al. 1995; Slieker et al. 1996). However, the effect of leptin on GC induction also depends on whether subjects are fed or fasted. GC/dexamethasone-induced upregulation of leptin is only observed when subjects are appropriately fed and not when they are fasted (Dagogo-Jack 1997; Laferrère et al. 1998). GCs possibly synergize with insulin (which is high only under fed conditions) to elevate plasma leptin levels (Laferrère et al. 2002). Increase in anorexigenic activity due to leptin production in a fasted state is likely not favorable for survival, which might be the reason why GCs induce leptin production only under a fed state. Leptin levels increase only when glucocorticoid levels are elevated as a result of the stress response (e.g., low temperature, carbon dioxide); however, in some studies, prolonged chronic stress does not cause change in glucocorticoids, possibly due to habituation of the HPA axis and maintenance of homeostasis, and hence does not result in increased leptin levels (Gamaro et al. 2008; Nakahara et al. 2010; Macedo et al. 2012; De Oliveira et al. 2014; Koelsch et al. 2016).

Leptin reduces GC production directly by suppressing several components of the HPA axis. Basal and stress-induced HPA activity is induced by the activity of CRF receptor type 1 (CRF_1R). Leptin infusion suppresses stress-induced upregulation of CRF_1R in the paraventricular nucleus (PVN) of rats subjected to 1-hour treadmill running (Huang et al. 2006; Stengel and Tachã 2014). Thus, leptin shuts down HPA activity initially by reducing CRF_1R expression in the hypothalamus. Interestingly, leptin has completely opposite effect on CRF receptor type 2 (CRF_2R). High leptin infusion in mice brain increases expression of CRF_2R in the ventromedial nucleus of the hypothalamus (VMN; Makino et al. 1998; Huang et al. 2006). CRF_2R can induce anorexia and the expression of CRF_2R is low in obese, food-deprived, and diabetic rats (with low plasma leptin levels or impaired leptin signaling; Richard et al. 1996; Timofeeva and Richard 1997). Thus, leptin's CRF-mediated anorectic activity involves the upregulation of CRF_2R in the VMN. Although there are conflicting reports on leptin's effect on direct CRF production from the PVN, the differential regulation of CRF receptors explains leptin's role in regulating hunger and HPA activity (Fig. 1; Costa et al. 1997; Heiman et al. 1997; Raber et al. 1997; Huang et al. 1998, 2006; Inui 1999; Yamagata et al. 2013). Leptin can decrease stress-induced plasma ACTH levels but there has been no evidence of direct action of leptin on pituitary ACTH in mammals, although leptin and leptin receptors are expressed in ACTH-producing cells in the anterior pituitary (Trottier et al. 1998; Oates et al. 2000; Lloyd et al. 2001; Howe and Gertler 2002; Yuen et al. 2004). In the adrenal gland, leptin downregulates melanocortin type 2 receptor (MC2R) mRNA expression in the zona fasciculata. MC2R binds specifically to ACTH to induce GC synthesis, and MC2R inhibition impedes GC production (Gorrigan et al. 2011; Su et al. 2012). Leptin resulted in a dose-dependent decrease in ACTH-induced cortisol production *in vitro* in human adrenocortical cells (Glasow et al. 1998). Leptin knockout mice were reported to have 85% higher GC levels than basal, and leptin injection into these knockouts reduced GC levels by 40% (Davis et al. 2015). Leptin further reduces adrenal GC synthesis by reducing expression of the steroid precursor cholesterol transporter (StAR) and steroid synthesizing enzymes 21-hydroxylase (*cyp21a2*) and side-chain cleavage enzyme (P450SCC) in cultured bovine adrenocortical cells (Kruse et al. 1998). Leptin does not have a local autocrine or paracrine action on adrenal glands as human adrenal glands do not express leptin mRNA but possibly express leptin receptor mRNA because adrenal gland cells obtained from leptin receptor knockout (db/db) mice do not show inhibitory action of leptin (Pralong et al. 1998; Glasow et al. 1998).

3. GC–leptin counterregulation during food intake and energy expenditure

GCs and leptin each regulate food intake and energy balance mostly in opposing ways. With respect to food intake, acute stress (within hours) suppresses appetite through activation of the anorexigenic CRF_2R in the

VMN but high levels of GCs as a result of prolonged chronic stress have been shown to induce hyperphagia (by increasing activity of orexigenic neurons AGRP and NPY), consequently increasing body weight and the susceptibility to obesity (Fig. 1; Dallman et al. 2006; Sominsky and Spencer 2014). Leptin is primarily known to suppress appetite and terminate GC-induced hyperphagia in three ways: (1) by increasing activity of anorexigenic CRF_2R, and POMC and CART neurons; (2) by decreasing activity of orexigenic AGRP and NPY neurons in the hypothalamus; and (3) by suppressing HPA axis activity thereby reducing further GC production (Fig. 1; Makino et al. 1998; Huang et al. 2006; Perry et al. 2019). Hence, the GC-induced direct upregulation of the anorexigenic hormone leptin is a potential mechanism to counterbalance GC-induced hyperphagia. Similarly, reduction in food intake and depletion of fat reserved results in a fall in leptin levels, which further allows GC levels to increase. Rise in GC levels would then stimulate appetite and increase in leptin levels postfeeding, ensuring efficient hormonal, and energy homeostasis.

Besides negatively regulating appetite, leptin and GCs also counterregulate lipolysis and lipogenesis, which eventually modulates energy expenditure and indirectly controls each other's plasma levels. During acute stress, GCs increase available energy by elevating plasma glucose levels by stimulating glycogen and protein catabolism in the liver and muscle and by lipolysis in adipocytes, however, during chronic stress GCs decrease lipolysis (Rebuffé-Scrive et al. 1992; Pantoja et al. 2008; Xu et al. 2009; Campbell et al. 2011; Stimson et al. 2017). *In vivo* and *in vitro* experiments show that GCs increase lipolysis when treated for 24–48 h at levels normally found in the plasma (Rebuffé-Scrive et al. 1992; Djurhuus et al. 2002; Campbell et al. 2011; Stimson et al. 2017; Mir et al. 2021). However, GCs can decrease lipolysis when treated at stress-induced levels and when the treatment time exceeds 48 h (Fig. 2; Fain and Saperstein 1970; Slavin et al. 1994; Xu et al. 2009; Campbell et al. 2011). In addition, GCs boost insulin-dependent *de novo* lipogenesis (the process of lipid synthesis from nonlipid substrates such as glucose) in liver and increase activity of lipoprotein lipase in adipocytes. Lipoprotein lipase promotes lipogenesis by releasing fatty acids from triglycerides circulating in the blood, which are obtainable for uptake and storage in adipocytes thereby enlarging adipose tissue deposits (Fig. 2; Diamant and Shafrir 1975; Berdanier 1989; Fried et al. 1993; Ottosson et al. 1994; Wang et al. 2004; Cai et al. 2009; Lee et al. 2011). Thus, prolonged GC exposure increases food intake which combined with reduced lipolysis and increased lipogenesis creates an overall positive energy balance which contributes to GC-mediated weight gain and obesity. The overall higher positive energy balance in terms of higher adipose tissue content potentially facilitates leptin production which then suppresses appetite and suppresses GC production. By facilitating lipolysis and reducing lipogenesis, leptin possibly antagonizes the anabolic actions of GCs on lipids, thereby demonstrating additional negative feedback between GCs and leptin. Based on pieces of evidence from *in vitro* studies, leptin upregulates lipolysis and downregulates *de novo* lipogenesis in white adipocytes by elevating the yield of triglycerides, restricting basal and insulin-stimulated *de novo* lipogenesis, and by accelerating oxidation of glucose and free fatty acids (Fig. 2; Bai et al. 1996; Wang et al. 1999; Ceddia and Curi 2002; Harris 2014; Koltes et al. 2017). Results from *in vivo* injection of leptin in rodents reinforce that leptin influences adipose tissue metabolism by elevating lipolysis, and by decreasing the activity of lipoprotein lipase and lipogenesis (Sarmiento et al. 1997; Zhou et al. 1999; Soukas et al. 2000). Leptin-induced fat reduction may also be accomplished by apoptosis in white adipose tissue as subcutaneous leptin treatment to ob^{-}/ob^{-} mice was reported to stimulate apoptosis in different fat depots (Qian et al. 1998; Della-Fera et al. 2003; Gullicksen et al. 2003; Della-Fera et al. 2005; Hamrick et al. 2006). In sum, increased lipolysis and reduced lipogenesis by leptin result in a fall in lipid levels, which then reduces leptin production, restores appetite, and normalizes GC production.

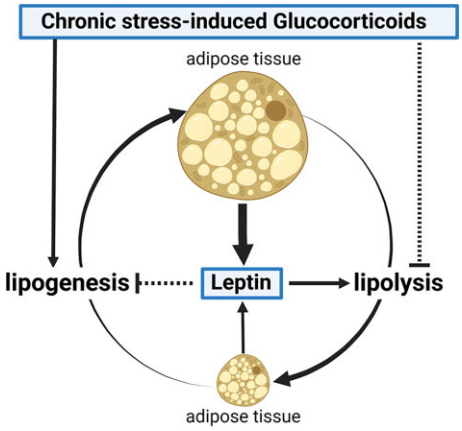

Fig. 2 Counterregulatory interaction between GCs and leptin in regulating lipid metabolism. Solid black lines: stimulatory effect; dashed black lines: inhibitory effect.

4. GC–leptin counterregulation during life-history transitions

The counterregulatory action of GCs and leptin exists during development but occurs mainly in the context of the surge in hormone levels. Fetal leptin and GC levels

rise and reach peak levels immediately before birth in mammals and drop at parturition (Campbell and Murphy 1977; Jaquet et al. 1998; Yura et al. 1998; Cetin et al. 2000; Lepercq et al. 2001; Mastorakos and Ilias 2003; Bolten et al. 2011; Rog-Zielinska et al. 2013). High levels of maternal progesterone act as the main source of high fetal GC levels. Maternal progesterone enters the fetal circulation and is converted into GCs by steroidogenic enzymes in fetal adrenal glands (only 10–20% of maternal GCs enter fetal circulation; Branchaud et al. 1986; Ingram et al. 1999; Ishimoto and Jaffe 2011; Wagner and Quadros-Mennella 2017). High GC levels then likely act to push leptin to reach peak levels as cortisol and dexamethasone infusion increases plasma leptin levels in fetal sheep (Forhead et al. 2002). In turn, this surge in leptin levels likely acts to suppress GC levels as in adults to achieve a new hormonal homeostasis during this developmental window. There are two key functions of such high titer of hormones during development. First, both leptin and GC surge are critical for the maturation of several organs, especially brain, lungs, and heart. Second, the leptin surge suppresses the HPA axis enough to prevent stress-induced elevation of GCs beyond levels considered normal for the surge. Leptin-mediated suppression of the HPA axis has an influential role in protecting neonatal organs from the harmful effects of excessive GCs by maintaining a period of reduced adrenocortical response to stress called the stress-hyporesponsive period (SHRP; Sapolsky and Meaney 1986; Yi and Baram 1994; Dent et al. 1999; Gunnar and Donzella 2002; Heinrichs et al. 2002; Tilbrook and Clarke 2006; Schmidt et al. 2009; Zelena et al. 2011; Ralph and Tilbrook 2016). SHRP is characterized by stable circulating levels of GC and the inability of the adrenocortical cells to produce additional GCs in response to certain mild to moderate stressors, which have been shown to stimulate profound ACTH and GC response in adults (Damato 1992; Cirulli et al. 1994; Levine 1994; Schmidt et al. 2002, 2003). Interestingly, SHRP continues beyond parturition postnatally when leptin levels start rising at the beginning of lactation in neonates reaching peak levels around mid-lactation and reduces to nonpregnant levels at weaning (Ahima et al. 1998; Johnstone et al. 2000; Slattery and Neumann 2008). However, GC levels drop below nonpregnant levels following parturition, maintain low basal levels, and do not start to rise to nonpregnant levels until around weaning when leptin levels start dropping (Voogt et al. 1969; Concannon et al. 1978; Schmidt et al. 2003; Maestripieri et al. 2008; Josefson and Skibiel 2021). The reason why leptin levels remain high during both prenatal and postnatal SHRP periods, but GC levels are low during postnatal SHRP is not known clearly but could involve other metabolic and neuroendocrine factors. Postnatal SHRP is not the result of changes in the HPA axis as the cause of SHRP could not be explained by reduced ACTH secretion, impaired signaling through MC2R, reduced activation of GC-secreting adrenocortical cells, or cholesterol unavailability (Proulx et al. 2001; Salzmann et al. 2004; Walker et al. 2004; Malendowicz et al. 2007). However, SHRP was concomitant with the downregulation of steroidogenic acute regulatory protein (StAR), 21-hydroxylase (*cyp21a2*), and peripheral-type benzodiazepine receptor (PBR; which transports cholesterol across the outer mitochondrial membrane; Walker et al. 2004). As mentioned in the section "GC-induced leptin upregulation and leptin-induced suppression of GC productionGC-induced leptin upregulation and leptin-induced suppression of GC production," leptin has been shown to downregulate steroidogenic enzymes in the adrenal gland in adults. Hence, it is likely that leptin-induced downregulation of steroidogenic enzymes in neonatal adrenal glands contributes to SHRP. The surges in leptin and GCs are contemporaneous, and additional leptin does not decrease baseline GC levels during prenatal and postnatal periods but does act to mitigate stress-induced increases in GC above the normal developmental surge level (Salzmann et al. 2004).

Some exceptions where SHRP can be disrupted include exposure to extreme stressors in the early postnatal period, such as low temperature, ether fumes, or prolonged maternal separation (>12 h), and increase in glucocorticoid production during SHRP (Viveros et al. 2010). Maternal separation of postnatal rodents for 12–24 h causes a drop in leptin levels and removes leptin's inhibitory effect on GC production leading to a sharp rise in GC and aldosterone (Salzmann et al. 2004; Viveros et al. 2010). Maternal separation of rat pups in postnatal day (PND) 10 increased protein expression of all steroidogenic enzymes in the adrenal glands (StAR, PBR, 3β-hydroxysteroid dehydrogenase, P450C11B1, and P450C11B2) beyond the maximum value of about 3–4 g/dl (generated by the majority of mild to moderate stressors), thus overriding adrenal hyporesponsivity (Shanks et al. 1999; Vázquez and Levine 2005). Thus, leptin terminates ACTH-stimulated or stress-induced production of GCs, by a rapid reduction in expression of StAR and PBR proteins in the neonatal/postnatal adrenal gland. As neonatal/postnatal leptin levels are modulated mostly by maternal diet, reduction in neonatal leptin levels followed by maternal separation is mostly due to lack of feeding. Lack of feeding during maternal separation disrupts several metabolic signals, including insulin and ghrelin levels, expression of AGRP, POMC, CART, and NPY neurons, and in several instances also modulate BDNF expression that can affect leptin production directly and

indirectly (Schmidt et al. 2006; Wang et al. 2020). Restoring tactile stimulation in addition to feeding the pups during the separation period prevents most of the peripheral and central consequences of maternal separation (Van Oers et al. 1998; Schmidt et al. 2006). Normalizing leptin levels during maternal separation failed to restore normal GC levels otherwise increased due to maternal separation but reduced ACTH-induced GC secretion, and StAR and PBR protein expression during maternal separation (Salzmann et al. 2004). These observations suggest that altered metabolic signaling during maternal separation results in a sharp fall in leptin level, which partly contributes to increased levels of GCs.

5. Implications of leptin–GC crosstalk on brain development

Between GCs and leptin, GCs have more established roles in brain development as evidenced from studies using rodents, primates, and humans. GCs are necessary for several critical steps in brain development, such as myelination, neurogenesis, gliogenesis, cell proliferation, and differentiation (Champagne et al. 2009; Moisiadis and Matthews 2014). However, high stress-related levels are deleterious to brain development, where prenatal stress before the onset of SHRP resulted in a significant reduction in neurogenesis in rhesus monkeys and rodents and a significant reduction in brain cell proliferation in rodents (Charil et al. 2010; Davis et al. 2013). In the adult human brain, leptin receptor is expressed in the cortex, amygdala, hippocampus, and thalamus, with the highest expression levels in the arcuate nucleus (ARC) and the PVN (Couce et al. 1997; Meister 2000). Gray matter density increases in regions associated with emotion, awareness, and motivation, such as the anterior cingulate gyrus, inferior parietal lobule, and the cerebellum when leptin-deficient humans are supplemented with leptin during adulthood (Matochik et al. 2005). At birth, leptin knockout and leptin receptor knockout mice have aberrant levels of growth-associated proteins and synaptic proteins, extensive neurotransmitter-related abnormalities, blunted myelination, and reduced brain weight, cortical volume, neuronal size, brain DNA content, and brain protein content (Ahima et al. 1999). Most of these aberrations in leptin knockout mice were corrected when leptin treatment was initiated at 4 weeks and not 9 weeks after birth, thus indicating that the perinatal influence of leptin on brain development is age-dependent (Steppan and Swick 1999). However, lack of leptin resulted in an unprecedented rise in GC levels and prolonged overexposure to GCs (up to 9 weeks) possibly causing extreme damage to the neonatal brain that cannot be reversed by subsequent leptin supplementation (Bouret and Simerly 2004; Lu 2007; Delahaye et al. 2008; Lewis et al. 2019; Steinbrekera et al. 2019). However, since leptin can strongly influence GC levels during development, it is not clear if reduced leptin or increased GCs were responsible for the altered brain phenotype in the leptin-deficient mice mentioned above.

Independent of GC–leptin regulation of each other's plasma levels, GC and leptin may interact at peripheral levels in brain cells containing receptors for both hormones. *In vivo* and *in vitro* studies in mice reported inhibition of leptin-dependent IL-1β expression in the hypothalamus by dexamethasone, possibly through modulation of leptin receptor expression (Smith and Waddell 2002; Hosoi et al. 2003). IL-1β functions through IL-1 receptor and IL-1 receptor signaling does not mediate the physiological effects of basal leptin signaling on energy balance. However, when leptin is administered at pharmacological levels, IL-1 receptor signaling is required for leptin-induced anorexia and weight loss (Wisse et al. 2007). Future investigations should focus on central as well as peripheral effects of GC–leptin interactions on fetal brain development because the extent to which an effect attributed to one hormone is actually due to its role in altering the signaling of the other hormone is not well understood. For example, neonatal rodent models studying the effect of GC overexposure on brain development should include a combination of GC overexposure and leptin supplementation to observe if leptin can override the negative effects of GCs on phenotypic and behavioral outcomes.

6. Implications of leptin–GC crosstalk on developmental programming

A large body of research shows that the risk of developing diseases in later life is contingent upon early life conditions (Gluckman et al. 2008; Vaiserman 2011; Haywarda et al. 2016; Maccari et al. 2017; Acevedo et al. 2021). Excessive GCs (from maternal stress and/or exogenous replacements) during the prenatal and early postnatal period are clearly linked to debilitating metabolic outcomes in adults, such as obesity, hyperglycemia, insulin resistance, leptin resistance, and diabetes mellitus (Grilo et al. 2021; Monica Shih et al. 2021; Sheng et al. 2021). GCs significantly govern developmental programming of the fetal brain as stress-induced neurological disorders during pregnancy such as anxiety and depression and exposure to stressful events such as a natural disaster, increase the susceptibility of the infant/child to developing emotional, behavioral, and cognitive abnormalities in adulthood (Ilg et al. 2018). With respect to leptin and developmental

programming, several animal models have demonstrated that leptin antagonism or overexposure in early life led to increased susceptibility to obesity and metabolic and developmental disorders in adulthood (Kirk et al. 2009; Granado et al. 2012; Vickers and Sloboda 2012). Leptin-knockout mice and pregnant rats with low leptin levels due to prenatal undernutrition demonstrated leptin resistance, hyperinsulinemia, and hypertriglyceridemia in adulthood (Krechowec et al. 2006). Administration of leptin reverses all these phenotypes in leptin-knockout mice (Chehab et al. 1996; Steppan and Swick 1999; Huang et al. 2008; Da Silva et al. 2017). Growth rate, body composition, and organogenesis were amended following neonatal leptin supplementation to female rats from malnourished mothers (Vickers et al. 2005; Attig et al. 2008). Leptin knockout mice also demonstrated reduced locomotor activity, and leptin receptor knockout mice displayed neurobehavioral anomalies similar to depression, anxiety, and psychosis (Sharma et al. 2010). Leptin receptor knockout mice had elevated levels of immune and inflammation-related compounds in the hippocampus concomitant with schizophrenia, autism-spectrum disorders, and bipolar disorder. Leptin supplementation at pharmacological doses during the first ten days of lactation in mice resulted in increase in anxiety-like behavior in adults (Fraga-Marques et al. 2009). Because plasma levels of GCs and leptin are tightly controlled by each other, studies on the development of adult metabolic disorders due to maternal stress or growth restriction should be conducted both in light of leptin deficiency and glucocorticoid overexposure. Perhaps leptin supplementation can override the harmful effects of GC overexposure or prenatal stress on the development of adult metabolic disorders.

7. Conclusion and future studies

In this review, we have summarized mechanisms of GC–leptin interactions and the possible effects those interactions on development. GCs and leptin are necessary to regulate appetite and energy expenditure, but chronic stress-induced GC levels can derail metabolic homeostasis. To maintain metabolic homeostasis, GCs upregulate leptin production that can suppress GC production directly. Each hormone also antagonizes each other's metabolic actions. This counterregulation between leptin and GCs to regulate metabolism is conserved across vertebrates. We have also suggested the importance of GC–leptin interdependence during fetal development. Adequate levels of leptin and GC are required for normal development of fetal organs, especially the brain. However, excessive GC levels from maternal stress and/or exogenous treatments negatively impact organogenesis causing several neurological, behavioral, and metabolic disorders. Leptin plays a crucial role in maintaining appropriate GC levels by regulating a period of stress hyporesponsiveness (SHRP) during which the adrenal gland is insensitive to most stressors. Withdrawal/reduction of the leptin levels during development due to maternal separation or maternal undernutrition may contribute to loss of SHRP and thus exposure of fetal organs to excessive GCs. *In vivo* studies tracking the long-term effects of maternal GC excess on the development of adult disorders did not fully account for the possible effects of altered leptin levels. Future studies should include the impact of leptin sufficiency/deficiency when investigating the mechanistic basis of GC excess on brain development and on the programming of adult diseases. Similarly, investigations focused on understanding leptin's role in organ maturation and developmental programming should account for GC excess and deficiency. The negative feedback loop between GCs and leptin has mostly been studied with respect to appetite regulations and metabolic homeostasis. Future studies should focus on understanding the role of leptin–GC counterregulation on growth, reproduction, and immune function.

Author contribution

Bidisha Paul: Conceptualization, Literature Review, Writing—original draft, Writing—review & editing. Daniel R. Buchholz: Conceptualization, Supervision, Writing—review & editing

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Conflict of interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Information included in the current manuscript can be obtained from the list of references.

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