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Review

Does altered glucocorticoid homeostasis increase cardiovascular risk?

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Abstract

The hypothalamic–pituitary–adrenal (HPA) axis, like the sympathetic nervous system and the renin–angiotensin–aldosterone (RAA) system, sustains life in stressful situations by increasing vascular tone and ensuring fuel availability. It also modulates inflammation and tissue repair processes. Untoward cardiovascular effects of chronic sympathetic and RAA activation are well recognized, illustrating that the short-term benefit of the physiologic stress response can be detrimental in the long term. Similarly, chronic tissue exposure to glucocorticoids may lead to metabolic and vascular changes that accelerate vascular senescence. Specific situations associated with chronic activation of the HPA axis—such as major depression, inflammatory disease and perhaps the metabolic syndrome—may derive some of their associated cardiovascular risk from untoward glucocorticoid effects. Since there are no definitive clinical studies directly addressing the relationship between the HPA axis and cardiovascular disease, we present indirect evidence from two types of studies: (1) studies that examine the cardiovascular effects of exogenous glucocorticoids, and (2) studies demonstrating that endogenous glucocorticoid activity varies between individuals. The effects of physiologic increases in endogenous glucocorticoid activity may not always mirror the effects of supraphysiologic glucocorticoids. Nevertheless, the known effects of exogenous glucocorticoids provide important insights into the putative effects of endogenous glucocorticoids.

Keywords: Hypothalamic–pituitary–adrenal axis; Glucocorticoids; Metabolic syndrome; Stress response

1. Introduction

The hypothalamic–pituitary–adrenal (HPA) axis is vital for survival in stressful situations such as hemorrhage and sepsis [1]. The primary glucocorticoid in humans, cortisol, is secreted continuously by the adrenal cortex in a diurnal pattern, with early morning peaks and evening troughs, but its release and effects are dynamic and increase dramatically in the setting of environmental stressors [2,3]. Glucocorticoid deficiency (resulting from pituitary or adrenal dysfunction) can result in hypotension, weight loss, hypoglycemia and death, especially in the setting of stress [4]. Conversely, glucocorticoid excess (resulting from endocrine adenomas or from pharmacologic treatment with glucocorticoids) can contribute to the development of hypertension, insulin resistance, hyperglycemia and weight gain [5,6]. Hence, grossly excessive or impaired cortisol secretion can adversely affect many bodily functions.

Normal glucocorticoid physiology can be summed up into three main roles. The first is to "prime" the metabolic, autonomic, psychological, hemostatic and cardiovascular components of the stress response in preparation for various stresses that may occur during the day [7]. These permissive actions facilitate the vascular and metabolic effects of other stress hormones, such as catecholamines, glucagon and angiotensin-II, through stimulation of alpha-1 adrenergic and angiotensin II receptor expression, and increasing the affinity and binding capacity of beta-adrenergic receptors [8–12]. The second role of glucocorticoids is suppressive. Glucocorticoids prevent inflammation, cellular proliferation

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and tissue repair processes from "overshooting" and leading to self-injury or circulatory collapse [7,13,14]. A third role of glucocorticoids is partitioning of body composition. Glucocorticoids prepare the organism for prolonged nutritional deprivation by facilitating proteolysis and insulin resistance at the level of the muscle [15–17]. However, insulin sensitivity and lipogenesis in fat depots are enhanced [18,19]. Because of the pleiotropic effects of glucocorticoids, it is probable that certain effects—such as increased blood pressure and insulin resistance—may harm the cardiovascular system, while other functions, such as suppression of inflammation and cellular proliferation, may be advantageous. However, it is likely that the net effects of increased glucocorticoid tone are harmful to the vasculature.

Epidemiologic studies suggest accelerated atherosclerosis in the presence of long-term excessive glucocorticoid exposure. Prior to surgical treatment of Cushing syndrome, it was not uncommon for these patients to experience early death from myocardial infarction or stroke [20]. In animal models, glucocorticoids can induce atherosclerosis [21]. Observational studies in humans suggest that corticosteroid-treated rheumatoid arthritis and lupus patients have significantly more atherosclerosis than those not treated with steroids and the risk of atherosclerosis is related to the cumulative dose of corticosteroids [22,23]; however, the extent of inflammation is an important confounder in the atherosclerosis associated with rheumatologic disease [24]. Additionally, there have been case reports of adverse outcomes of steroid-dependent rheumatoid arthritis patients treated with thrombolytic agents for acute myocardial infarction, perhaps due to increased risk of myocardial rupture [25]. However, there is no consensus that glucocorticoids are harmful if given acutely in the setting of myocardial infarction [26].

2. Tissue regulation of glucocorticoid function

Glucocorticoids readily diffuse through cellular membranes and exert their effects by binding to intracellular receptors of two types. Type I receptors are mineralocorticoid receptors (MR) and type II receptors are the classic glucocorticoid receptors (GR). Both receptors reside in the cytoplasm in the inactivated state. Once activated by glucocorticoid binding, the GR enters the nucleus. The GR is ubiquitous, accounting for the widespread effects of glucocorticoids. The activated GR influences nuclear transcription directly by binding to DNA, enhancing or inhibiting gene transcription via interaction with the promoter regions of glucocorticoid-responsive genes (so-called glucocorticoid response elements). Glucocorticoids also exert effects by interacting with protein transcription factors without binding to DNA directly [13,27,28]. This indirect mechanism appears to account for most of the anti-inflammatory effects of glucocorticoids [13].

The response of a tissue to glucocorticoids depends on two main factors: intracellular hormone concentrations and differential receptor expression and function. Intracellular hormone levels are affected by adrenal glucocorticoid secretion, exogenous glucocorticoid exposure and the intracellular metabolism of cortisol [13,29]. In some tissues, such as the kidney, the enzyme 11-beta hydroxysteroid dehydrogenase II (11-beta HSD II) converts cortisol to inactive cortisone, allowing aldosterone to bind to its receptor without competition from high concentrations of cortisol; deficiency of this enzyme, as seen in apparent mineralocorticoid excess syndrome, results in renal-mediated congenital hypertension [30,31]. The enzymatic counterpart, 11-beta HSD I, re-activates cortisone to cortisol [32] and is present in many tissues, including fat, liver, muscle and vascular endothelium [33–38]. The deactivation and activation of cortisol by 11-beta-HSD enzymes allows for tissue-specific glucocorticoid effects by modulating the concentration of glucocorticoids present in the active or inactive forms.

Tissue sensitivity to glucocorticoids is dynamic. For example, the effects of exogenous hydrocortisone on glucose metabolism and insulin kinetics are more dramatic when hydrocortisone is given in the evening, when endogenous glucocorticoid levels are usually low, than when given in the morning, when endogenous glucocorticoid levels are high [39].

GR variants, namely the Bcl1 restriction fragment length polymorphism and the N363S variant, have been described and have been associated with Cushingoid features, hypertension, visceral obesity and hyperinsulinemia. Recently, Lin et al. [40] reported that the N363S variant was four times more frequent in those with obstructive coronary artery disease (CAD) and five times more frequent in those with both obesity and CAD than in controls.

3. Inter-individual variability in HPA axis and glucocorticoid tone

Methods to characterize the activity of the HPA axis include measurements of plasma or salivary cortisol levels at specific times of day, 24-h urinary excretion of cortisol (or metabolites) and response of the HPA axis to exogenous glucocorticoids, ACTH or CRH analogues. These tests can identify severe HPA axis pathology (e.g., Cushing or Addison disease) but are often unable to differentiate between varying levels of glucocorticoid tone in the general population. More technically challenging methods of assessing glucocorticoid tone that are used in the research setting include serial measurements of diurnal fluctuations in cortisol [41], low-dose dexamethasone suppression testing, and measuring tissue concentrations of glucocorticoid receptors and tissue activity of 11-beta-HSD isoenzymes [42–44]. These techniques have provided evidence that glucocorticoid tone varies between individuals, even in the absence of a defined endocrinopathy.

Sustained physiological stress, such as starvation, leads to substantially increased circulating cortisol levels throughout the day [45,46]. Similarly, sustained caloric restriction in rodents is associated with elevated glucocorticoid levels [47,48]. Increased glucocorticoid activity in the setting of starvation may be adaptive—preventing hypoglycemia and slowing fuel utilization. However, subtle variation in glucocorticoid activity may be apparent in other conditions, and may not always be adaptive: Depressed patients have higher circulating glucocorticoid levels and have impaired suppression of cortisol in response to dexamethasone [49]; these abnormalities resolve with treatment of the depression [50]. Many depressed patients also exhibit signs of increased glucocorticoid tone: central obesity, menstrual irregularity, immunosuppression and osteoporosis [51]. Elderly patients tend to have slightly higher levels of circulating cortisol than younger patients and may exhibit a blunted circadian amplitude of cortisol secretion [52,53]. Patients with high waist-to-hip ratios also may have blunted diurnal patterns of cortisol secretion [41] and impaired cortisol suppression in response to low-dose dexamethasone [54]. Twenty-four-hour secretion of cortisol metabolites may be elevated in the metabolic syndrome as compared to controls [55].

In a study of healthy elderly men and women, Huizenga et al. showed that the suppression of cortisol in response to low-dose dexamethasone had marked inter-individual variation. A significant correlation between baseline response to dexamethasone and the response 2.5 years later demonstrated relative intra-individual stability, suggesting that individuals may have HPA tone "set points" [56]. Even healthy young men have significantly different responses to dexamethasone suppression testing [57]. Suggested causes of inter-individual variability in HPA tone include low birth weight [58], stress [59], visceral obesity [60] and age-related changes in the axis [52].

At the tissue level, the regeneration of cortisol from cortisone in adipose tissue (via 11-beta HSD I) depends upon body mass index, cytokine exposure, insulin-like growth factor-1 (IGF-1) activity and insulin levels [33,34,61–63], and may therefore vary between individuals with different levels of inflammation, insulin sensitivity, growth hormone activity or obesity. In skeletal muscle, human glucocorticoid receptor concentrations and 11-beta-HSD I expression may be positively correlated with insulin resistance, obesity and hypertension [64,65].

Given these observations, it is likely that some individuals have higher glucocorticoid tone than others, especially in particular tissue beds. Glucocorticoid tone, like blood pressure, heart rate, cholesterol levels, body mass index or sympathetic tone, may be a predictor of cardiovascular risk, even if it is difficult to measure in a given patient at a given time. We have come to recognize the extent to which high sympathetic tone and high RAS tone adversely impact cardiovascular disease by observing the benefits of beta-adrenergic blockers and drugs that block the RAS. To date, however, we have no such evidence that pharmacological glucocorticoid blockade has salutary cardiovascular effects. Glucocorticoid receptor blockade and interference with adrenal glucocorticoid production have been attempted only on a limited basis, due to poor efficacy or unacceptable toxicity [66]. For example, systemic treatment with the GR antagonist mifepristone leads to compensatory increases in cortisol [67], which, by activity at MRs might attenuate the benefit of GR blockade. Similarly, other compensatory mechanisms, such as increased ACTH, renin and angiotensin II, may mitigate prolonged cardiovascular benefits of aminoglutethimide [68,69], returning cortisol levels to pre-treatment levels after several days [70]. Compensatory increases in ACTH may blunt salutary effects of glucocorticoid blockade via direct lipid effects [71], direct vascular effects [36] and increased mineralocorticoid production [72]. Although ACE inhibitors may modulate tissue cortisol metabolism as a secondary mechanism of action [73], it is unknown whether specific blockade of tissue glucocorticoid activity (such as blockade of 11-beta-HSD-mediated cortisol regeneration) will have clinical benefits [42].

4. Effects of excess glucocorticoids on specific cardiovascular risk factors

4.1. Body composition

Fat cells are metabolically active, secreting hormones, cytokines and metabolites that adversely affect blood pressure, plasma lipoproteins, coagulation and insulin resistance [74]. Any metabolic change that leads to obesity, particularly its visceral component, may thereby increase cardiovascular risk. In the presence of insulin, glucocorticoids promote terminal differentiation of pre-adipocytes and fibroblast-like stromal vascular precursor cells into mature adipocytes [75,76]. Glucocorticoids and insulin act synergistically to increase the activity of adipocyte lipoprotein lipase [77], freeing lipids in circulating lipoproteins for storage in fat cells. Glucocorticoids and insulin also increase the activity of 11-beta-HSD I in adipocytes, especially in visceral fat depots [62], potentially augmenting abdominal obesity in the setting of high insulin and glucocorticoid activity. Transgenic mice with increased 11-beta HSD-1 activity in adipocytes exhibit obesity and associated adverse metabolic complications [78]. Desensitization in adipocytes to the lipolytic effects of catecholamines may also contribute to visceral adiposity with long-term increases in glucocorticoid exposure [79]. However, the insulin resistance that accompanies chronic elevated glucocorticoid exposure may result in visceral adipocytes that are less sensitive to the antilipolytic action of insulin, contributing to elevated circulating free fatty acid levels (Fig. 1; Table 1) [79,80].

Increased visceral adiposity and decreased muscle mass are features of aging in humans, and may result, in part, from increased glucocorticoid activity coupled with

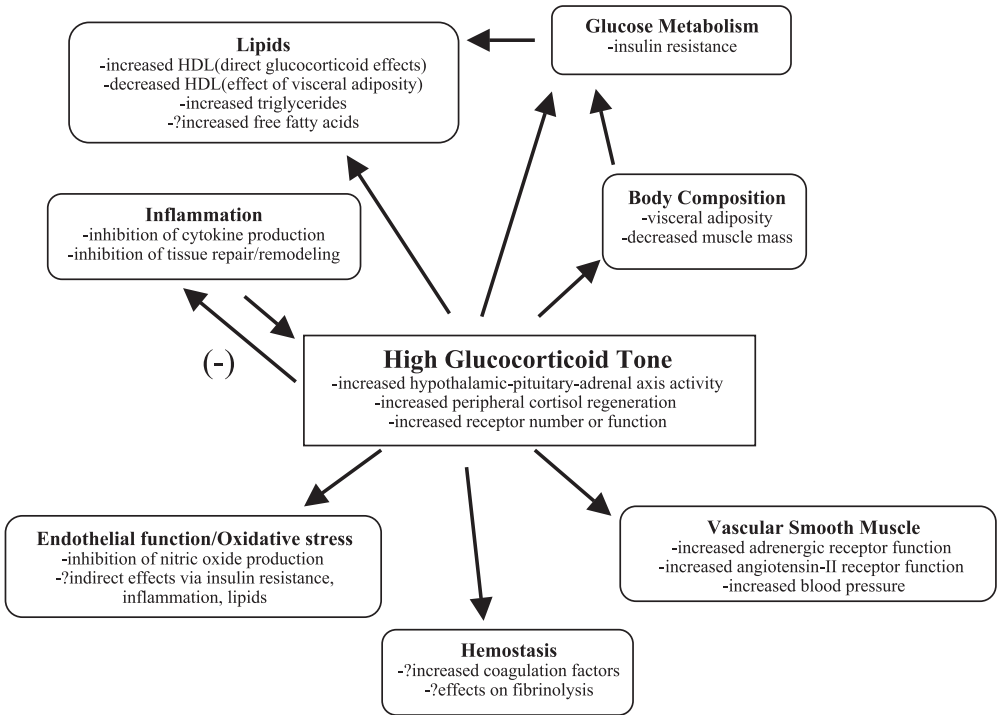

Fig. 1. Glucocorticoid effects on various cardiovascular risk factors.

decreased growth hormone and IGF-1 activity [81,82]. Visceral obesity may be apparent in depressed younger patients as well, perhaps due in part to chronic hypercortisolemia and glucocorticoid-mediated tissue effects [2].

4.2. Plasma lipoprotein metabolism

Obesity of any etiology can have ill effects on plasma lipoproteins, and obesity from glucocorticoid exposure is no exception [5]. Visceral obesity, in particular, is associated with low high-density lipoprotein cholesterol (HDL-C), high triglyceride levels and small and dense low-density lipoprotein cholesterol (LDL-C) particles [83,84]. Glucocorticoids also have direct effects on circulating lipids and lipoproteins, increasing LDL-C, triglycerides and HDL-C. Lipid changes can occur within 48 h of the initiation of prednisone treatment and therefore cannot be attributed to changes in adiposity; these increases in total cholesterol, LDL-C and HDL-C are sustained in long-term follow-up [85,86]. Prednisone-treated patients with systemic lupus erythematosis (SLE) also have elevated apolipoprotein B levels [87].

Glucocorticoids decrease the concentration of LDL-C receptors on hepatocytes [88] leading to higher LDL-C levels. Glucocorticoid administration leads to hypertriglyceridemia through increased production and secretion of very low density lipoprotein (VLDL) from the liver [89]. The increase in HDL-C associated with glucocorticoids may be due to increased apolipoprotein-A synthesis by the liver, and may mitigate some of the adverse effects of increased LDL-C and triglycerides [90].

4.3. Carbohydrate metabolism

Glucocorticoids lead to muscle and hepatic insulin resistance and can precipitate hyperglycemia [7]. Human and animal studies have helped elucidate the mechanisms for acute glucocorticoid-induced insulin resistance including stimulation of hepatic gluconeogenesis and decreased muscle glucose uptake. In the liver, glucocorticoids oppose the actions of insulin and activate gluconeogenesis by increasing acetyl coenzyme-A levels; this leads to feedback inhibition of the pyruvate dehydrogenase complex (PDH), stimulation of pyruvate carboxylase (PC) and phosphoenol pyruvate carboxykinase (PEPCK). Glucocorticoid-induced increases in citrate concentrations augment feedback inhibition of glycolysis [91]. In rat skeletal muscle, exogenous glucocorticoids cause carbohydrate-related insulin resistance by inhibition of GLUT 4 transporter recruitment to the cell surface [92], and by decreasing insulin receptor substrate (IRS-1) levels [93]. The thiazolidinediones are insulin sensitizers that may oppose many of these metabolic pathways and are effective in treating glucocorticoid-induced diabetes mellitus [94].

4.4. Endothelial function and oxidative stress

Endothelial dysfunction often precedes atherosclerosis and is associated with impaired nitric oxide (NO) production, perturbed interactions between platelets, leukocytes and the vessel wall, and alterations in thrombosis and thrombolysis [95,96]. Endothelial dysfunction can be

Table 1
Effects of glucocorticoids on cardiovascular risk factors and atherosclerotic mediators

Risk factor/mediator	Effect	Evidence	Reference
Metabolic			
Visceral obesity	Increase	Human adipocytes in vitro	[75–77]
		Animals in vivo	[78]
Low-density lipoprotein cholesterol	Increase	Healthy humans in vivo	[85]
High-density lipoprotein cholesterol	Increase	Healthy humans in vivo	[86]
Triglycerides	Increase	Healthy humans in vivo	[89,90]
Insulin resistance/glucose intolerance	Increase	Healthy humans in vivo	[7,94]
Vascular tone/oxidative stress			
Blood pressure	Increase	Healthy humans in vivo	[10]
Endothelial function	Impaired	Healthy humans in vivo	[98]
NADH/NADPH oxidase	Variable	Human vascular cells in vitro	[103]
Inducible nitric oxide synthase	Decrease	Human and animal endothelial cells in vitro	[99]
Endothelial nitric oxide synthase	Variable	Human in vitro	[100,102]
Endothelin-1	Increase	Animal vascular endothelial cells in vitro	[105]
Endothelin-1 receptor	Decrease	Animal vascular smooth muscle cells in vitro	[106,107]
Angiotensinogen	Increase	Human adipocytes in vitro	[8]
		Animal adipocytes in vitro	[110]
Angiotensin-converting enzyme	Increase	Animal vascular smooth muscle cells in vitro	[108,109,111]
Angiotensin II type I receptor	Increase	Animal vascular smooth muscle cells in vitro	[108,109]
Alpha-1 adrenergic receptor	Increase	Animal vascular smooth muscle cells in vitro	[108,109]
Prostacyclin E2	Decrease	Animal vascular smooth muscle cells in vitro	[108,109,111]
Hemostasis			
Platelet activator inhibitor-1	Increase	Human adipocytes in vitro	[113,114]
Von Willebrand factor	Increase	Human endothelial cells in vitro	[112]
Inflammation			
Cellular adhesion molecules ICAM-1, ELAM-1	Decrease	Human endothelial cells in vitro	[125]
Plasma matrix metalloproteinases MMP-2, 9	Decrease	Healthy humans in vivo	[123]
Circulating cytokines IL-1,2, 6 and TNF-alpha	Decrease	Depressed humans in vivo	[119]
		Rheumatoid arthritis humans in vivo	[120]
C-reactive protein	Increase	Human hepatocytes in vitro	[128]
	Variable	Animals in vivo	[129,130]
	Decrease	Rheumatoid arthritis humans in vivo	[135]

precipitated by hyperglycemia, hypertension and dyslipidemia, all of which are well-known effects of chronic glucocorticoid exposure [97]. Cortisol administration to healthy normotensive men may also impair cholinergic vasodilation directly [98]. This may be mediated in part by reduced activity of inducible nitric oxide synthase (iNOS) [99] or by increased oxidative stress. Oxidative stress may be especially pronounced with prolonged glucocorticoid exposure [100].

Endothelial function is closely tied to the degree of tissue oxidant stress. Three major sources of reactive oxygen species include uncoupling of the endothelial nitric oxide synthase (eNOS), xanthine oxidase and NADH/NADPH oxidase [101]. In vitro, glucocorticoids may indirectly stimulate eNOS and release of NO [102], but may decrease eNOS mRNA stability [100]. Patients with Cushing syndrome may have increased nitrotyrosine levels (a measure of increased oxidative stress) in vascular tissue and decreased brachial artery reactivity [103]. Human umbilical vein endothelial cells exposed to dexamethasone generate reactive oxygen species via stimulation of NADPH oxidase and xanthine oxidase [103]. However, prednisolone and hydrocortisone downregulate NADPH oxidase in human aortic vascular smooth muscle cells in vitro [103], and the effects of glucocorticoids on xanthine oxidase have been inconsistent [100]. Furthermore, since oxidative stress is often coupled to inflammation [104] and glucocorticoids have potent anti-inflammatory effects, it is plausible that glucocorticoids can indirectly reduce oxidative stress by suppression of inflammation (discussed below).

Glucocorticoids also may stimulate release of the potent vasoconstrictor endothelin-1 [105], however, this effect may be counterbalanced by a compensatory decrease in endothelin-1 receptors [106,107].

4.5. Vascular tone

Glucocorticoids also increase vascular tone by endothelial-independent mechanisms. Dexamethasone increases blood pressure in healthy adults by increasing total peripheral resistance, whereas fludrocortisone (a selective mineralocorticoid) increases blood pressure by increasing

cardiac output [10]. Glucocorticoids augment vascular tone through permissive actions, enhancing the activity of adrenergic stimulation, angiotensin II and possibly endothelin-1. Glucocorticoids up-regulate angiotensin II type I receptor expression and alpha-1 adrenergic receptors in rat vascular smooth muscle cells and potentiate the vasoconstrictive actions of angiotensin-II and norepinephrine in animals [108,109]. Glucocorticoids may also increase hepatic and adipocyte production of angiotensinogen [8,110], increase ACE expression and activity, and reduce prostacyclin E2 synthesis in endothelial cells and vascular smooth muscle cells [108,109,111]. All of these actions may underlie the known adverse effects of glucocorticoids on blood pressure.

4.6. Hemostasis

Although there are no in vivo studies in humans demonstrating that glucocorticoids directly affect hemostasis, there is in vitro and epidemiologic evidence of this phenomenon. In cultured human umbilical vein endothelial cells, dexamethasone increases production of von Willebrand Factor (vWF), endothelin and PAI-1 [112]. Two studies have demonstrated dexamethasone-mediated increases in PAI-1 in cultured human adipose tissue [113,114]. In patients with Cushing syndrome, elevated levels of vWF, PAI-1, thrombin–antithrombin and plasmin–antiplasmin complexes and factor VIII may resolve after curative surgical treatment [115–117].

4.7. Inflammation and tissue repair

Atherosclerosis is, in part, an inflammatory disease of the subendothelium [118]. The relationships between glucocorticoids, inflammation and vascular disease are complex. In some clinical settings, acute administration of glucocorticoids is associated with decreased circulating levels of IL-6 and CRP [119,120]. Similarly, short-term glucocorticoid exposure attenuates many of the known mediators of vascular lesions: cellular adhesion molecule expression (ICAMs, selectins), monocyte chemotaxis and phagocytosis, LDL oxidation, T-cell activation, collagen and extracellular matrix deposition, smooth muscle proliferation and matrix metalloproteinase activity [121–125]. However, these acute anti-inflammatory effects may wane with long-term glucocorticoid exposure [126]. On the other hand, glucocorticoid administration elicits a leukocytosis [119,127], and cytokines such as TNF-alpha, IL-6 and IL-1 are elaborated by adipocytes and may be increased in the setting of obesity. Glucocorticoids also may directly augment the production of some cytokines at the gene transcription level. Dexamethasone potentiates IL-6-induced CRP release by in vitro human hepatic cells [128]. In some animal models, ACTH and prednisolone may increase CRP [129] by over 50-fold, but this has not been confirmed in other animal models [130] or in humans. Despite short-term decreases in IL-6 with glucocorticoid administration, in prolonged stress the adrenal gland may be a major source of IL-6 [131]. One study in rats showed stress-induced systemic IL-6 levels to decrease by 80% with adrenalectomy [132].

Cytokines appear to activate the HPA axis [133]. IL-6 directly stimulates the hypothalamus to secrete corticotrophin-releasing hormone (CRH), anterior pituitary cells to secrete ACTH, and the adrenal cortical cells to secrete cortisol [118,132]. Incubation of adrenal cells with IL-6 in vitro causes a dose-dependent increase in cortisol [132]. This suggests that IL-6 is a major link between the HPA axis and inflammatory system. In fact, it has been suggested that IL-6 is the "tissue CRH" because of its stimulation of glucocorticoid secretion, especially in chronic stress situations [134,135]. This phenomenon may contribute to the observed correlation between CRP and serum cortisol in patients with active rheumatoid arthritis [136].

5. Clinical implications and future directions

The harmful effects of chronic sympathetic nervous system and renin–angiotensin–aldosterone (RAA) system activation were not fully appreciated until beta-adrenergic blockers and ACE inhibitors achieved widespread clinical use and were subjected to randomized prospective trials. The same may prove true for the HPA axis. Although some drugs, such as thiazolidinediones, fibrates and ACE inhibitors, target certain glucocorticoid-responsive genes [73,137–140], there are no drugs in widespread use that specifically block glucocorticoid effects as their primary mode of action or specifically modulate HPA axis tone. Potential drug targets may include 11-beta-HSD enzymes and other enzymes that modulate tissue effects of glucocorticoids [141,142]. Potential target populations for such treatments may include patients with depression, chronic illness, or visceral obesity. With renewed research interest in the vascular and metabolic effects of glucocorticoids, we may soon come to realize that glucocorticoids, like other stress hormones, accelerate cardiovascular senescence.

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