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Review

Intra-vascular glucocorticoid metabolism as a modulator of vascular structure and function

P. W. F. Hadoke*, L. Macdonald, J. J. Logie, G. R. Small, A. R. Dover and B. R. Walker

Endocrinology Unit, Centre for Cardiovascular Science, Edinburgh University, The Queen's Medical Research Institute, 47, Little France Crescent, Edinburgh, EH16 4TJ, Scotland (United Kingdom), Fax: +44 (0) 131 242 6779, e-mail: phadoke@staffmail.ed.ac.uk

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Abstract. The ability of glucocorticoids to directly alter arterial function, structure and the inflammatory response to vascular injury may contribute to their well-established link with the development of cardiovascular disease. Recent studies have emphasised the importance of tissue-specific regulation of glucocorticoid availability by the 11β-hydroxysteroid dehydrogenase (11HSD) isozymes, which inter-convert active glucocorticoids and their inactive metabolites. The expression of both type 1 and type 2 11HSDs in the arterial wall suggests that pre-receptor metabolism of glucocorticoids may have a direct impact on vascular physiology. Indeed there is evidence that 11HSDs influence glucocorticoid-mediated changes in vascular contractility, vascular structure, the inflammatory response to injury and the growth of new blood vessels. Hence, inhibition of 11HSD isozymes may provide a novel therapeutic target in vascular disease.

Key words. 11β-Hydroxysteroid dehydrogenase; inflammation; vascular contractility; angiogenesis; cardiovascular disease.

Introduction

There is increasing evidence that direct interaction of glucocorticoids with the vascular wall [1, 2] contributes to their association with increased risk of cardiovascular disease [3, 4]. Certainly, glucocorticoids can interact both with endothelial (EC) and with vascular smooth muscle (VSMC) cells, and furthermore, glucocorticoid-mediated enhancement of vascular contractility has been implicated in the development of hypertension [5]. In addition, glucocorticoids may directly modify new blood vessel formation and vascular lesion development by inhibiting inflammation, proliferation and angiogenic pathways in the arterial wall [6, 7].

Interaction of glucocorticoids with the vasculature is unlikely to be regulated solely by circulating concentrations of these steroids; pre-receptor metabolism within target tissues also has a profound influence on glucocorticoid activity. Such tissue-specific modulation of glucocorticoid activity, regulated by the isozymes of 11β-hydroxysteroid dehydrogenase (11HSD) [8], has a key role, for example, in the development of hypertension, obesity and the metabolic syndrome [9–11]. It is likely that pre-receptor metabolism of glucocorticoids influences steroid action within the vessel wall since both isozymes of 11HSD are expressed in vascular cells [12]. This article reviews the current evidence that vascular 11HSD expression influences glucocorticoid-mediated changes in vascular growth, function, structure and the inflammatory response to vascular injury.

Glucocorticoid signalling in the vascular wall

Glucocorticoids (cortisol in man, corticosterone in rodents) are predominantly synthesised in, and released

* Corresponding author.

from, the adrenal cortex. Circulating concentrations of these steroids are under the control of the hypothalamic-pituitary-adrenal (HPA) axis, whilst their bioavailability is regulated by interaction with corticosteroid-binding globulin (CBG) and albumin in the plasma. The small proportion of unbound, circulating hormone is able to cross the cell wall and interact with corticosteroid receptors. Classically, glucocorticoids interact with the cytosolic glucocorticoid receptor (GR, or corticosteroid receptor type II). As described below, glucocorticoids may also activate mineralocorticoid receptors (MR, or corticosteroid receptor type I), but this occurs only in a few tissues. GR and MR are members of the nuclear hormone receptor superfamily of ligand-activated transcription factors [13]. Activation of GR results in binding of receptor homodimers to glucocorticoid response elements in target genes, leading to initiation or repression of transcription. There is also increasing evidence that glucocorticoids exert specific, non-genomic actions. Examples exist of rapid glucocorticoid-induced changes to phospholipase A_2 (PLA_2) and phosphoinositide-3-kinase-mediated endothelial nitric-oxide synthase (eNOS) release that are blocked by GR antagonism but not by inhibition of transcription [14, 15]. These non-genomic effects are thought to be mediated by membrane-bound GR [16] (mGR; although the specific signalling pathways associated with these receptors have not been established) or by cytosolic GR (cGR) without requirement for either nuclear translocation or effects on transcription. In the latter case, chaperones or co-chaperones (such as Src) act as signalling components and, therefore, mediators of glucocorticoid-induced effects [17].

Corticosteroid receptors are present in the cells of the vascular wall, supporting the idea that glucocorticoids interact directly with the vasculature. Cytosolic MR and GR have both been demonstrated in freshly isolated vessels [18, 19] and in cultured vascular cells (VSMCs [20, 21] and ECs [22–26]) from a variety of species. The distribution of these receptors may vary with vascular territory, as MR were detected in rabbit aortic and pulmonary VSMCs but not in small arteries [27]. Vascular GR are known to be active as antagonism (with RU38486) blocked dexamethasone-mediated induction of ACE activity in rat aortic ECs [28]. Similarly, activity of MR is demonstrated by their contribution to angiotensin II-induced hypertrophy of VSMCs [29] and aldosterone-induced swelling of ECs [22]. It has not been established whether membrane binding sites for corticosteroids are present, or have a role, in the vascular wall.

The downstream effects of GR activation within the arterial wall, and their influence on cardiovascular risk factors (such as hypertension), are imperfectly understood [5]. Glucocorticoids are essential for maintenance of blood pressure in healthy individuals [1], whilst their ability to increase peripheral vascular resistance in animals devoid of renal mass indicates that a non-renal mechanism contributes to glucocorticoid-induced hypertension [30]. A considerable body of evidence suggests that this non-renal mechanism may involve direct glucocorticoid-mediated alteration of EC and VSMC function [1]. Consequently, regulation of glucocorticoid availability by 11HSDs within the vascular wall may be an important influence on cardiovascular physiology and pathology.

Tissue-specific metabolism of glucocorticoids by 11β-hydroxysteroid dehydrogenases

The 11HSDs, microsomal enzymes of the short-chain alcohol dehydrogenase superfamily [8], interconvert active glucocorticoids and their inert 11-keto forms [31]. Two isozymes, 11HSD1 and 11HSD2, have been identified: 11HSD1 is a low-affinity NADP(H)-dependent, predominant reductase *in vivo*. Dehydrogenase activity of this isozyme is generally not seen in intact cells or organs (including liver [32–34], adipose tissue [35], neurons [36] and vascular smooth muscle [37]); early suggestions of 11HSD1 dehydrogenase activity in vascular smooth muscle [38] are probably attributable to 11HSD2 [37]. 11HSD1 dehydrogenase activity observed in some preparations *in vitro* [39] is probably attributable to release of enzyme from damaged or dying cells, with dissociation from hexose-6-phosphate dehydrogenase, which is thought to maintain the high NADPH concentrations required for reductase activity [40]. 11HSD1 has a Km in the micromolar range for both cortisol and corticosterone [41] and is widely expressed in glucocorticoid-target tissues (including liver, lung, adipose tissue, brain, vascular smooth muscle, skeletal muscle, anterior pituitary, gonads and adrenal cortex [8]), where its role is to amplify local glucocorticoid concentrations [42]. Regulatory control of 11HSD1 is complex, with its synthesis and activity influenced by a variety of factors (such as glucocorticoids [43–45], stress [46, 47], sex steroids [48], growth hormone [49], cytokines [50] and peroxisome proliferator-activated receptor agonists [8]) and its activity driven in the reductase direction through local generation of NADPH by hexose-6-phosphate dehydrogenase [51]. Other factors that may drive 11HSD1 activity in the reductase direction include the cellular environment, co-factor availability, redox potential and substrate concentration.

11HSD2, by contrast, is a high-affinity NAD-dependent, exclusive dehydrogenase, which converts active glucocorticoids into inactive 11-ketosteroids and has a Km for cortisol and corticosterone in the nanomolar range. It is found primarily in mineralocorticoid target tissues, such as the kidney, sweat glands, salivary glands and colon 8], where it is constitutively active and serves to protect MR

from illicit occupation by glucocorticoids. Inhibition of 11HSD2 with liquorice or its derivatives results in glucocorticoid-dependent 'apparent' mineralocorticoid excess and hypertension [52]. Similarly, transgenic disruption of 11HSD2 [9] in mice, or congenital deficiency in man [53], recapitulates the major features of the syndrome of apparent mineralocorticoid excess (SAME). The importance of 11HSD2 in SAME was demonstrated by the description of a defect in cortisol metabolism in children with this syndrome [54]; this was later shown to be the result of mutations in the 11HSD2 gene [55, 56]. 11HSD2 is also expressed in tissues which are not classic MR targets, including the lung, lymph nodes, heart, blood vessel wall and placenta) [57–59]. In the placenta 11HSD2 acts to protect the foetus from excessive exposure to maternal glucocorticoids [60, 61], whereas cardiac 11HSD2 activity may have a role in preventing fibrosis resulting from stimulation of MR by glucocorticoids [62].

The influence of 11HSD isozyme activity on cardiovascular physiology and pathophysiology is well recognised (see Krozowski and Chai for review [63]), but details of the role of 11HSDs within the vessel wall have emerged only recently and remain somewhat uncertain.

Intra-vascular glucocorticoid metabolism

Both isozymes of 11HSD are expressed in the blood vessel wall, suggesting that they could influence vascular function by regulating local availability of active glucocorticoids [1, 64]. The cellular distribution of vascular 11HSD1 and 11HSD2 is not completely clear. Our studies using mouse and rat aorta suggest that 11HSD2 is localised to ECs, whereas 11HSD1 is predominantly in the VSMC (fig. 1) [18, 65]. Others, in contrast, have reported activity of both enzymes in the VSMC [37, 50] and also in the EC [66], it should be noted that the latter investigation [66] demonstrated only 11HSD1 in rat VSMC and indicated that 11HSD1 was the predominant isozyme in the endothelium. Direct comparison of studies is often difficult, given the use of arteries from different species and anatomical locations combined with a variety of techniques for detecting 11HSDs. The balance of the literature suggests that cellular distribution of 11HSD isozymes differs in vessels from distinct anatomical locations and that 11HSD activity increases as artery diameter diminishes; in the rat 11HSD, activity was greater in resistance (mesenteric) arteries than in conduit vessels (aorta) [65] and in the mouse 11β-reductase activity was higher in iliofemoral arteries than in the aorta [A. R. Dover et al., unpublished data]. These variations in cellular distribution and activity suggest that the role of intravascular glucocorticoid metabolism is not the same in all blood vessels.

There is increasing evidence that interconversion of active and inactive glucocorticoids by vascular cells may influence glucocorticoid-mediated modulation of vascular function, structure, growth and inflammation.

Glucocorticoids, 11HSDs and vascular function

Although it is well established that glucocorticoids contribute to maintenance of vascular tone *in vivo,* the mechanisms have been difficult to establish. A variety of interactions contribute to homeostasis, including glucocorticoid-mediated regulation of cardiac output and fluid and electrolyte balance, with salt and water handling modulated both directly [67] and indirectly by influences on the production of angiotensinogen (liver), arginine vasopressin (AVP; hypothalamus) [68] and atrial natriuretic peptide (ANP; cardiac myocytes) [69]. It is apparent, however, that these cardiac and renal effects cannot account totally for the glucocorticoid-mediated increase in blood pressure, and there is evidence that a component of hypertension arises from enhanced contractility of the vascular wall [70–72]. For example, reversal of adrenocorticotophin-dependent hypertension by administration of l-arginine (the substrate for nitric oxide synthase) suggests that nitric oxide deficiency contributes to the elevation of blood pressure [73, 74].

Glucocorticoid-dependent potentiation of noradrenaline- and angiotensin II-mediated vasoconstriction has been at-

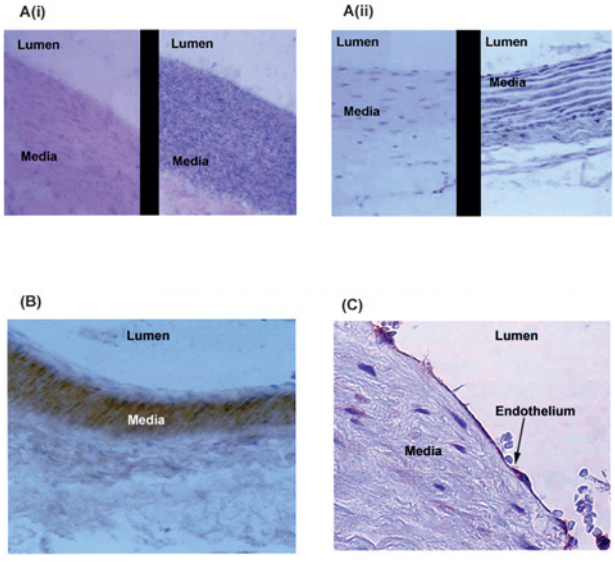

Figure 1. Presence and distribution of 11HSD isozymes in the vascular wall. *In situ* hybridisation (*Ai*) and immunohistochemistry (*Aii*) confirming both expression and activity of 11HSD1 within the rat aortic wall; the enzyme was predominantly localised to medial smooth muscle cells (left-hand panel, sense/control; right hand-panel, antisense/antibody to 11HSD1). Immunohistochemistry demonstrating (*B*) 11HSD1 in rat mesenteric artery smooth muscle and (*C*) 11HSD2 in human intra-renal artery endothelium [unpublished]. Reproduced from [65] with permission. © The Endocrine Society, 1991.

tributed to alterations within the VSMC and the EC (reviewed in Walker and Williams [2] and Ullian [1]). Given that glucocorticoids can act on both MR and GR, the increased contractility observed in many studies may be secondary to increased stimulation of either receptor. Alterations identified within the VSMC (including upregulation of contractile receptors, altered intracellular second messenger activation and modulation of the activity and synthesis of vasoactive substances) result in a direct enhancement of contraction [1]. In contrast, changes in the endothelium can increase contractility in two distinct ways: by increased release of vasoconstrictor compounds (e.g. angiotensin II, endothelin-1 [75, 76]) from the ECs and by impaired endothelium-mediated relaxation. Loss of endothelium-mediated relaxation [77], caused by impaired activity of vasodilators (e.g. prostaglandins, nitric oxide) [78–80], [reduces the ability of the endothelium to modulate contraction.

An alternative mechanism through which glucocorticoids may regulate vascular function is 'foetal programming' of physiological responses [81]. Exposure of the foetus to excess maternal glucocorticoid (either by direct infusion or by inhibition of placental 11HSD2) causes reduced birth weight [82], an outcome associated with increased risk of cardiovascular and metabolic disease in adulthood [83]. Two major causes of low birth weight, maternal dietary restriction and maternal stress, may also be glucocorticoid-dependent [84, 85]. In the ovine foetus, glucocorticoid infusion elevates blood pressure and alters vascular contractility in foetal sheep [86]; this may be significant, as one outcome of foetal programming is elevated blood pressure in adult offspring [87]. However, although enhanced vascular contractility has been demonstrated in rats with programmed hypertension, it is not clear whether this contributes to the elevation of blood pressure [88, 89]. Furthermore, the mechanisms through which pre-natal exposure to excess glucocorticoid programme enhance contractility in adult offspring have not been established.

Influence of 11HSDs on vascular function

In SAME, 11HSD2 deficiency results in sodium retention and severe hypertension, mediated in part by glucocorticoid-dependent activation of MR in the distal nephron [90]. There is, however, a considerable literature to suggest that changes in 11HSD activity within the vascular wall also contribute to elevation of blood pressure. A clear example of this is the demonstration that 11HSD activity is impaired in arteries taken from rat models of hypertension [91–93]. A role for altered vascular function is supported by reports that 11HSD inhibition (with glycyrrhetinic acid) in rats produced an elevation of blood pressure which, whilst mediated by MR activation, was blocked by antagonists of the endothelin-1 system [94, 95]. Moreover, studies of dermal vasoconstriction in patients exposed to liquorice, and in a single individual with SAME [53, 96], demonstrated enhanced cortisol-mediated constriction (fig. 2). The possibility that this is due to changes in glucocorticoid metabolism within the vascular wall, rather than indirect systemic effects of sodium retention, gained further credence with *in vitro* studies which showed that bile acids (e.g. chenodeoxycholic acid), which are endogenous inhibitors of 11HSD [97], pharmacological inhibitors of 11HSD (carbenoxolone, glycyrrhetinic acid) [98, 99] and isozyme selective antisense oligonucleotides [100] alter corticosterone-mediated enhancement of vasoconstriction. Furthermore, 11HSD inhibition (with glycyrrhetinic acid) augmented corticosterone-induced dysfunction in cultured human ECs, indicating both a role for intra-cellular 11HSD and independence from blood pressure elevation *in vivo* [95]. Care is required in interpreting these results, however, as some 11HSD inhibitors can directly alter contractile function by damaging the endothelium [101].

These pharmacological studies have been extended by the use of arteries from 11HSD knockout mice. Aortic function (and blood pressure) are unaltered in 11HSD1$^{-/-}$ mice suggesting that intravascular regeneration of active glucocorticoids has no effect on vascular contractility [102, 103]. This indicates that despite the ability of glucocorticoids to enhance vascular contraction, impaired corticosterone generation in the arterial wall does not re-

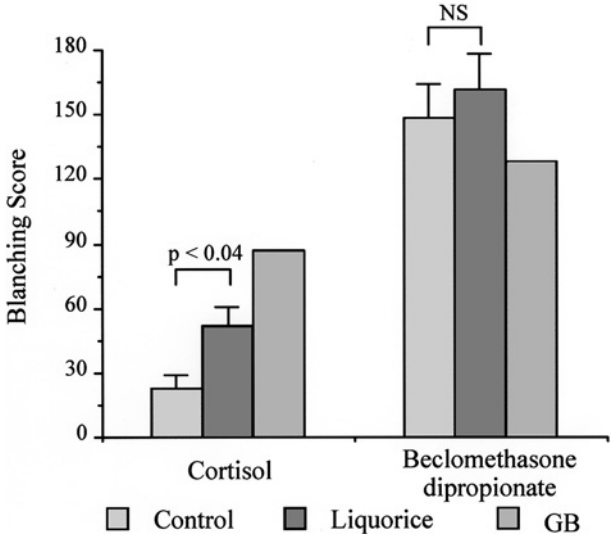

Figure 2. The effect of congenital and acquired 11HSD deficiency on dermal vasoconstrictor sensitivity to cortisol and beclomethasone dipropionate. Inhibition of 11HSD activity with liquorice-enhanced dermal vasoconstriction (measured by skin blanching) in response to cortisol but not to beclomethasone diproprionate. A similar result was obtained in a patient (GB) with the syndrome of apparent mineralocorticoid excess type 1 (11HSD2 deficiency). These data indicate that local regulation of glucocorticoid activity in the vascular wall contributes to contractile tone. Bars are s.e. NS, not significant. Reproduced from [53] with permission. © The Biochemical Society, 1992.

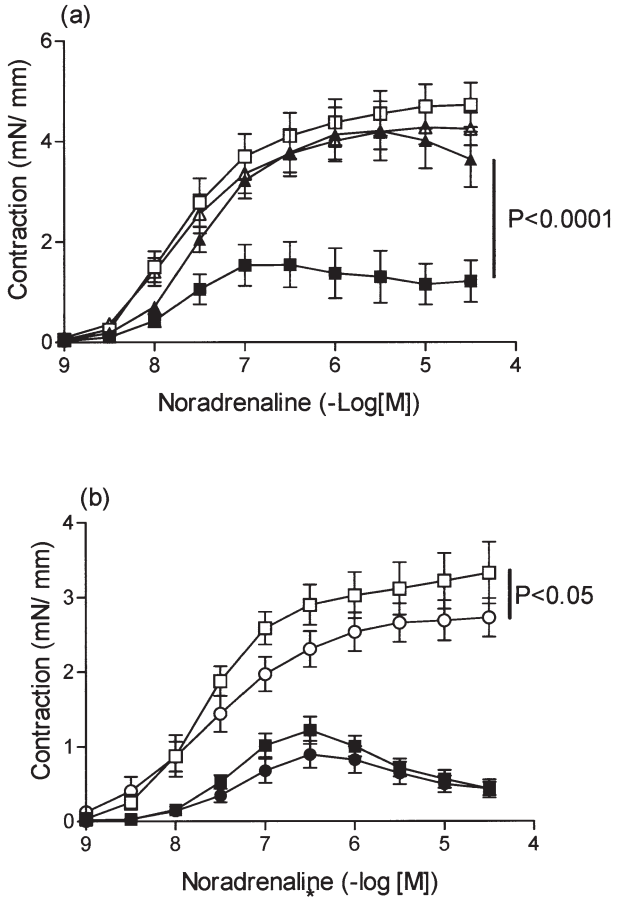

Figure 3. Effect of (*a*) transgenic deletion of 11HSD2 and (*b*) exposure to glucocorticoids on mouse aortic endothelial cell function. In aortic rings isolated from control mice (squares), release of endothelium-derived nitric oxide acts as a physiological antagonist of noradrenaline-mediated contraction; thus, removal of the endothelium (open symbols) results in enhanced contraction. In aortae from $11HSD2^{-/-}$ mice (*a*; triangles) this ability of the endothelium to modulate contraction has been lost, suggesting glucocorticoid-mediated impairment of endothelial cell function. This is contested, however, by the demonstration that (*b*) *in vitro* incubation (24 h, 37 °C; 10^{-7} M corticosterone) of aortic rings from control animals with glucocorticoids (circles) did not produce a similar endothelial cell dysfunction. Values are mean ± s.e. mean; n=8. Adapted with permission from [103] and [18]. © Lippincott, Williams and Wilkins.

duce contractile function. In contrast, enhanced contractility was demonstrated in thoracic aortae from mice lacking 11HSD2 as a result of impaired endothelium-derived NO activity [103], rather than changes in the VSMC (fig. 3a). This suggests that 11HSD2 activity in the endothelium may serve to protect endothelium-dependent relaxation from the detrimental effects of glucocorticoids. This appears to be consistent with *in vivo* studies which suggest that non-selective inhibitors of both isozymes of 11HSDs, such as liquorice derivatives, potentiate rather than impair the vascular actions of glucocorticoids, suggesting inhibition of inactivation rather than reactivation of steroids within the vessel wall. More recent data, however, suggest that the concept of protection of ECs by 11HSD2 may be an oversimplification. In mouse aortic rings, we could not induce EC dysfunction by incubating isolated rings with glucocorticoids (fig. 3b), even in the absence of 11HSD2 [18]; whether dehydrogenase activity of 11HSD1 [38] served to protect the endothelium is not clear, although our data suggest that 11HSD1 does not act as a dehydrogenase in intact arteries. This raises the possibility that *in vivo* differences in vascular function in 11HSD2 knockout mice are dependent on indirect mechanisms, e.g. related to hypertension or sodium retention. Cell-specific manipulation of 11HSDs would be the most attractive means to dissect this biology further, but has yet to be reported for vascular cells.

Glucocorticoids, 11HSDs and vascular inflammation

Whereas studies in transgenic mice have suggested that 11HSD2 activity may influence vascular function, whilst 11HSD1 does not, a much clearer role for 11HSD1 has been identified in regulation of vascular inflammation. The anti-inflammatory and immunosuppressive effects of glucocorticoids, which account for their most common therapeutic applications, are due to GR-mediated interactions with blood vessels, inflammatory cells and mediators of inflammatory responses [104]. For example, glucocorticoids decrease expression of adhesion factors, cytokines and chemokines, and so alter the recruitment of immune cells such as neutrophils and macrophages to sites of inflammation. This also results in a decrease in leukocyte activation and proliferation. Furthermore, the glucocorticoid receptor mediates lymphocyte apoptosis [105] and suppresses the synthesis of inflammatory mediators (e.g. prostanoids), and hydrocortisone stimulates the synthesis of anti-inflammatory mediators (e.g. lipocortins) [106]. Glucocorticoids, but not mineralocorticoids, can also promote the phagocytosis of apoptotic leukocytes [107], and so contribute to the resolution of inflammation. The expression of 11HSD1 in VSMCs [50] and in activated macrophages [108] suggests that generation of glucocorticoid within these cells may contribute to regulation of inflammation.

Influence of 11HSDs on vascular inflammation

The demonstration that pro-inflammatory cytokines selectively upregulate 11HSD1 activity in human VSMCs suggests that glucocorticoid generation within the vascular wall provides a mechanism for local feedback regulation of inflammation [50]. However, this has not been examined *in vivo*. The ability of inflammatory mediators to regulate 11HSD activity in VSMCs may be dependent upon the phenotypic state of the cells (with enzyme ac-

tivity upregulated in actively proliferating, but not in quiescent, cells), the anatomical origin of a particular vessel, the prevailing local glucocorticoid concentrations and the modulation of the inflammatory response by neighbouring tissues [A. R. Dover et al., unpublished data]. Further work is required to clarify the significance of cytokine-mediated regulation of 11HSD1 in arterial cells, particularly given the importance of inflammation in the vascular response to injury [109].

Alternatively, 11HSD1 may regulate inflammation by controlling generation of glucocorticoids within the inflammatory cells. Certainly, the ability of inflammatory cytokines to upregulate 11HSD1 activity in activated human macrophages [108] suggests, as in human VSMC [50], a means of feedback regulation of inflammation within these cells.

Glucocorticoids and vascular remodelling

The term 'vascular remodelling' has been used to cover a range of structural changes in the arterial wall, and its correct definition is the subject of debate (for review see Bund and Lee [110]). In this review, the term 'vascular remodelling' encompasses medial hypertrophy (thickening of the vessel wall caused by increase in cell size) and hyperplasia (thickening of the cell wall caused by an increase in cell number), as well as the intimal remodelling seen in neointimal proliferation and the development of atherosclerotic lesions. It has also been extended to include angiogenic growth of new blood vessels.

The relationship between glucocorticoids and arterial remodelling is well-established; for example, one year following remission, patients with Cushing's syndrome show reduced intimal/medial thickness and increased lumen diameter in the carotid artery [111]. It should be noted, however, that remodelling may be the indirect result of systemic changes (e.g. increased blood pressure) rather than direct interactions of glucocorticoids with the vessel wall. Glucocorticoids may induce vascular remodelling by altering expression of genes for relevant growth factors or by inhibiting processes that modulate growth factor activity. For example, dexamethasone induces a GR-dependent upregulation of endothelin-1 expression [76], and cortisol attenuates the activity of nitric oxide [77] (itself a potent inhibitor of cell growth). Similarly, dexamethasone- and hydrocortisone-mediated increases in ACE activity in VSMCs [112] and ECs [75] may enhance local generation of angiotensin II (a stimulant of VSMC growth both *in vitro* [113] and *in vivo* [114]).

Hypertrophy

Vascular hypertrophy in rats exposed to mineralocorticoids, predominantly deoxycorticosterone acetate, and salt [115] has been attributed to upregulation of the endothelin-1 gene [116]. Similarly, glucocorticoids (dexamethasone, hydrocortisone) have the ability to induce vascular hypertrophy by augmenting the production of [112, 117], and hypertrophic response to [118, 119], angiotensin II. The significance of this hypertrophy is unclear, however, as many investigations that demonstrate enhanced vascular contractility in response to corticosterone involved a duration of exposure that would be insufficient for vascular hypertrophy to occur [120]. Furthermore, glucocorticoid-mediated stimulation of growth in the vascular wall is counterintuitive given that dexamethasone inhibits VSMC growth in culture [121–123] and glucocorticoids prevent neointimal hyperplasia (see below). Thus, the direct influence of glucocorticoids on vascular hypertrophy/hyperplasia is unclear, and any role of local glucocorticoid metabolism by 11HSDs in the process has yet to be investigated.

Neointimal proliferation

The development of neointimal lesions (e.g. in atherosclerosis and in restenosis following revascularisation) is a consequence of an excessive wound healing response in the vessel wall [124, 125]. Vascular injury results in infiltration by inflammatory cells and subsequent migration and proliferation of VSMCs [109]. Consequently, inhibition of either the inflammatory response [126] or VSMC proliferation/migration [127] inhibits lesion development in a variety of models. Since glucocorticoids (dexamethasone) can inhibit inflammation and VSMC proliferation [121–123] and migration [128], it is not surprising that their potential as anti-atherosclerotic [129] and anti-restenotic agents [130] has been investigated [6]. It is also possible, however, that the action of glucocorticoids on the vessel wall is deleterious in patients with vascular disease. For example, given that ACE inhibition limits neointima formation following balloon injury [131, 132], stimulation of ACE activity by dexamethasone [75, 112] could exacerbate lesion development. Also, inhibition of endothelium-derived nitric oxide activity by glucocorticoids could increase both VSMC proliferation and vascular contraction. Further, the systemic effects of glucocorticoids on cardiovascular risk factors (glucose, insulin, lipids and blood pressure) may offset beneficial effects within the vessel wall.

Dexamethasone reduces cholesterol ester accumulation in the aorta [133], and glucocorticoids (dexamethasone, hydrocortisone) inhibit neointimal lesion formation in rats [134, 135], rabbits [136–138] and dogs [139] (with a few contradictory reports [140, 141]). Clinical trials in humans, by contrast, have proved disappointing (with notable exceptions [130]): methylprednisolone did not inhibit restenosis after coronary angioplasty [142] or stent implantation [143], whilst the combination of a glucocor-

ticoid with colchicine increased the risk of coronary aneurysm following stent placement [144]. Discrepancies between clinical studies and animal models could be attributed to species differences or, more probably, to methodological variation (e.g. small sample size; inappropriate patient selection, dose, duration of treatment, route of administration). Exacerbation of lesion development by glucocorticoids could be explained by systemic effects (e.g. weight gain with elevated blood pressure and plasma lipids, which may be more prominent in humans than in other species) or by a net stimulation of vascular cell proliferation. Alternatively, changes in plasma lipids could influence the ability of glucocorticoids to interact with vascular cells. Lipoprotein(a) can downregulate GR gene expression in human VSMCs, thus inhibiting any protective actions of glucocorticoids and, possibly, representing a novel atherogenic mechanism [145].

Angiogenesis

Angiogenesis, in which new blood vessels are formed from an existing vascular network, is a complex process regulated by a balance between counteracting endogenous activators and inhibitors [146]. Physiological angiogenesis is an essential component of reproduction and embryonic development. In postnatal and adult life, it is a discrete process (e.g. in the reproductive tract, wound healing and exercised skeletal muscle) of relatively short duration [147]. In contrast, pathological angiogenesis is usually persistent and unabated and often continues for months or years [147]. Numerous disorders are characterised by excessive angiogenesis, including neoplasia, rheumatoid arthritis and diabetic retinopathy [148]. Consequently, modulation of angiogenesis is regarded as an attractive therapeutic goal in a variety of conditions.

A comprehensive review of the mechanisms of angiogenesis is beyond the scope of this article (for recent reviews see [146, 149]). For the present purposes it is useful to consider angiogenesis to be a stepwise process comprising four distinct phases: (i) basement membrane disintegration, (ii) endothelial cell migration, (iii) channel formation and (iv) maturation. Of the numerous factors that control this process, vascular endothelial cell growth factor (VEGF) is widely considered to be of central importance, since it is crucial for vascular development both in the embryo and in adult tissues and it is EC specific.

Since its first demonstration by Folkman and colleagues, over 20 years ago [150], the ability of glucocorticoids to inhibit angiogenesis has been confirmed *in vitro, in vivo* and in tumour-bearing animals [150]. It was suggested that inhibition of angiogenesis in the rabbit cornea was independent of classical GR and MR activity [151]. For example, 17α-hydroxyprogesterone and tetrahydro-S, which have no glucocorticoid or mineralocorticoid activity, retained an anti-angiogenic capability equivalent to, or greater than, that of hydrocortisone. Taken together, these studies demonstrated a class of steroids for which inhibition of angiogenesis appears to be the principal function and hence were named 'angiostatic steroids.' [151].

Despite considerable research, the mechanisms through which glucocorticoids inhibit angiogenesis have not been identified. Indeed, the role of GR is still controversial, as some of the 'angiostatic steroids' may actually have the ability to stimulate these receptors. For example, we have recently shown that inhibition of angiogenesis by tetrahydrocorticosterone, one of the original angiostatic steroids, is dependent upon GR activation in mouse aortic ring explants [G. R. Small et al., unpublished]. Some indication of mechanism was provided by early studies which demonstrated, using nude mice or the non-anticoagulant hexasaccharide fragment of heparin, that the combination of glucocorticoid and heparin was independent of an immune response and anti-coagulant function, respectively [150]. At present, however, there are still several possible pathways through which glucocorticoids may inhibit angiogenesis: (i) Degradation of extracellular matrix, (ii) modification of cytokine production, (iii) inhibition of protease activity, (iv) impairment of vessel maturation and stabilisation, (v) inhibition of growth factor activity, (vi) inhibition of the arachidonic acid cascade, (vii) inhibition of EC-leukocyte interactions and (viii) non-transcriptional effects. The relative significance of these pathways has not been established.

11HSDs and vascular remodelling

Although the initial focus was on 11HSD2 and vascular function, the most recent work in the field of intra-vascular glucocorticoid metabolism has highlighted novel roles for 11HSD1 in influencing vascular structure and remodelling.

Neointimal remodelling and atherogenesis

The potential link between atherosclerosis and tissue-specific generation of glucocorticoids by 11HSDs has been underlined by recent demonstrations that selective upregulation of 11HSD1 in the adipose produces features of the metabolic syndrome, including central obesity, hypertension and hypertriglyceridaemia [10, 152]. This supports the concept that similarities between the metabolic syndrome and Cushing's syndrome are explained by tissue-specific increases in 11HSD1 activity resulting in tissue-specific elevation of glucocorticoid generation [153]. This link between 11HSD1 activity in glucocorticoid-target tissues and atherosclerotic risk factors is not limited to the adipose, as hepatic overexpression of 11HSD1 also results in elevated blood pressure and dyslipidaemia

[154]. It has been proposed, therefore, that 11HSD1 inhibition may reduce atherogenesis. Very recently, systemic administration of a selective 11HSD1 inhibitor was reported to virtually abolish lipid accumulation in the aorta of atherosclerotic (apolipoprotein $E^{-/-}$) mice. However, inhibition of 11HSD1 in $ApoE^{-/-}$ mice produced only a relatively modest reduction in serum triglycerides and cholesterol [155], suggesting that mechanisms over and above amelioration of systemic cardiovascular risk factors may be responsible. It may be that inhibition of 11HSD1 within the vessel wall or within invading macrophages [156] is crucial, but these mechanisms require further clarification.

11HSD2-dependent protection of MR from inappropriate occupation by glucocorticoids may also influence atherogenesis. The role of MR activation in the pathogenesis of atherosclerosis [157] is demonstrated by aldosterone-induced enhancement of lesion development in atherosclerotic (apolipoprotein $E^{-/-}$) mice (probably by increasing oxidative stress in macrophages and cells of the vascular wall [157, 158]). This potentiation of lesion development by aldosterone, which is largely independent of blood pressure, is attenuated by MR antagonists [157], as is constrictive remodelling following angioplasty [159].

The potential importance of 11HSD activity to the development of atherosclerotic lesions was recently extended by the demonstration that, in addition to glucocorticoid metabolism, 11HSDs catalyse the conversion of the atherogenic oxysterol 7-ketocholesterol to 7β-hydroxycholesterol [160]. 7-Ketocholesterol is present in micromolar concentrations in human atherosclerotic lesions and in nanomolar concentrations in the plasma [161]. Its

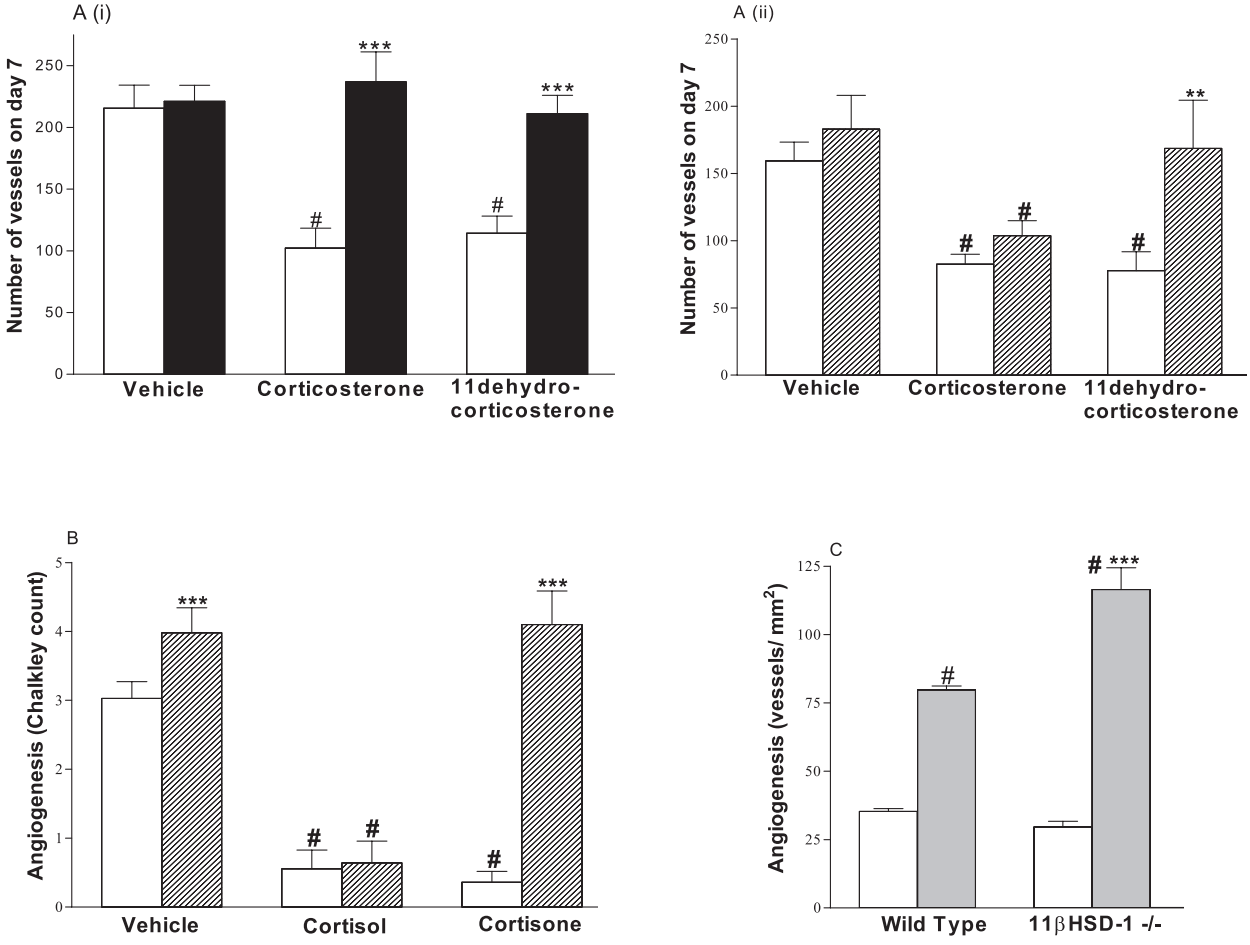

Figure 4. The influence of 11HSD1 on glucocorticoid-mediated angiogenesis. (*A*) In mouse aortic rings cultured in Matrigel, corticosterone and its inactive metabolite 11-dehydrocorticosterone attenuated new vessel growth. Glucocorticoid receptor antagonism (with RU38486, filled columns) abolished the angiostatic response to both compounds (*Ai*), but 11HSD1 deletion (hatched columns) selectively prevented 11-dehydrocorticosterone-mediated angiostasis (*Aii*). Similar results were obtained *in vivo*, using subcutaneous sponge implants (*B*), with 11HSD1 deletion (hatched columns) increasing angiogenesis under basal conditions and abolishing cortisone-, but not cortisol-, mediated inhibition of vessel growth. This mechanism contributed to regulation of myocardial angiogenesis following coronary artery ligation (*C*) with increased vessel growth in $11HSD1^{-/-}$ mice (coronary artery ligation, shaded bars; sham, open bars). $^{\#}p < 0.05$ compared with relevant vehicle-treated control; $^{**}p < 0.01$ compared with wild-type mice; $^{***}p < 0.001$ compared with relevant wild-type control or sham-operated mouse. Reproduced with permission from [168]. © The National Academy of Sciences of the USA, 2005.

association with atherosclerosis is demonstrated in the condition cerebrotendinous xanthomatosis, in which patients who have normal circulating cholesterol levels but increased 7-ketocholesterol develop atherosclerosis prematurely [162]. Conversion of 7-ketocholesterol to 7β-hydroxycholesterol by 11β-HSD1 may represent the rate-limiting step in a clearance pathway: *in vivo* inhibition of 11HSD1 in rats resulted in an accumulation of 7-ketocholesterol in the liver and increased concentrations in the plasma [163]. In addition to these hepatic effects, reduction of 7-ketocholesterol by 11HSD1 within the vascular wall may also be important. 7-Ketocholesterol and 7β-hydroxycholetserol are both toxic to cells of the vascular wall [164] and are potent inhibitors of endothelium-dependent relaxation [165–167]. Consequently, reduction of 7-ketocholesterol, and subsequent clearance of 7β-hydrocholesterol, by protecting the vascular wall from damage may have a role in preventing lesion development.

The influence of 11-HSD activity on angiogenesis

Since inflammatory cytokines can promote angiogenesis, we hypothesised that 11β-HSD1 in the vessel wall may regulate new vessel formation by controlling the local regeneration of active glucocorticoids. This possibly was addressed using a combination of *in vitro*, *in vivo* and pathological models of angiogenesis [168]. Using a model of tube formation from mouse aortic rings cultured in Matrigel [169], we demonstrated (fig. 4A) that angiogenesis was inhibited by physiological concentrations of active glucocorticoid (corticosterone) but also by its inactive metabolite (11-dehydrocorticosterone). Both these responses were blocked by RU38486, but not by spironolactone, indicating GR dependence. However, whereas 11HSD1-inhibition (with carbenoxolone) or deletion (aortic rings from 11HSD1$^{-/-}$ mice) had no effect on the response to corticosterone, they abolished the ability of 11-dehydrocorticosterone to inhibit angiogenesis (fig. 4B). This indicated that 11HSD1-dependent regeneration of active glucocorticoid within the vascular wall regulates new vessel growth. Application of a model of angiogenesis in sub-cutaneous sponge implants, confirmed this role for 11HSD1 *in vivo*, showing that 11HSD1 deletion produced increased angiogenesis in untreated sponges and blocked the ability of cortisone (but not cortisol) to inhibit new vessel formation. The pathophysiological significance of these observations was emphasised in healing cutaneous wounds and in the myocardial response to coronary artery ligation (fig. 4C). In both cases, 11HSD1 deletion resulted in increased angiogenesis, demonstrating that 11HSD1 regulates the growth of new blood vessels in healing tissues.

Altered angiogenesis in 11HSD1$^{-/-}$ [168] mice could, conceivably, be the result of changes in macrophage activity. Given that 11HSD1 is expressed in macrophages [170], and regeneration of glucocorticoids enhances phagocytosis of apoptotic neutrophils [107], absence of 11HSD1 may confer a prolonged and enhanced acute inflammatory response, thus stimulating angiogenesis. The use of *ex vivo* models such as isolated aortic rings cultured in extracellular matrices [171] has made it possible to differentiate between these two intimately related pathways, angiogenesis and inflammation, and specifically address the effects of glucocorticoids on angiogenesis in the absence of a systemic response. This has produced evidence that glucocorticoids regulate angiogenesis by direct interaction with the vessel wall [168].

Conclusions

It is apparent that glucocorticoids have the ability to regulate both the structure and the function of the artery wall, with significant implications for vascular physiology and pathophysiology. Emerging evidence suggests that pre-receptor metabolism of glucocorticoids within vascular ECs and VSMCs provides a mechanism for regulating these interactions. Relatively few studies have addressed the role of intravascular 11HSD activity, and most of those available have focussed on vascular function. There is, however, a growing body of evidence to suggest that 11HSD isozymes within the arterial wall modulate vascular contractility, the angiogenic growth of new blood vessels, and the atherosclerotic process. Whether these isozymes also influence the inflammatory response to vascular injury and the inter-conversion of atherogenic oxysterols in vascular smooth muscle has still to be determined. Further clarification of the role of 11HSDs in vascular cells is likely to increase our understanding of the link between glucocorticoids and a variety of vascular diseases, and to demonstrate their potential as therapeutic targets for treatment of these conditions.

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