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REVIEW

Therapeutic manipulation of glucocorticoid metabolism in cardiovascular disease

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The therapeutic potential for manipulation of glucocorticoid metabolism in cardiovascular disease was revolutionized by the recognition that access of glucocorticoids to their receptors is regulated in a tissue-specific manner by the isozymes of 11β-hydroxysteroid dehydrogenase. Selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 have been shown recently to ameliorate cardiovascular risk factors and inhibit the development of atherosclerosis. This article addresses the possibility that inhibition of 11β-hydroxsteroid dehydrogenase type 1 activity in cells of the cardiovascular system contributes to this beneficial action. The link between glucocorticoids and cardiovascular disease is complex as glucocorticoid excess is linked with increased cardiovascular events but glucocorticoid administration can reduce atherogenesis and restenosis in animal models. There is considerable evidence that glucocorticoids can interact directly with cells of the cardiovascular system to alter their function and structure and the inflammatory response to injury. These actions may be regulated by glucocorticoid and/or mineralocorticoid receptors but are also dependent on the 11β-hydroxysteroid dehydrogenases which may be expressed in cardiac, vascular (endothelial, smooth muscle) and inflammatory (macrophages, neutrophils) cells. The activity of 11β-hydroxysteroid dehydrogenases in these cells is dependent upon differentiation state, the action of pro-inflammaotory cytokines and the influence of endogenous inhibitors (oxysterols, bile acids). Further investigations are required to clarify the link between glucocorticoid excess and cardiovascular events and to determine the mechanism through which glucocorticoid treatment inhibits atherosclerosis/restenosis. This will provide greater insights into the potential benefit of selective 11β-hydroxysteroid dehydrogenase inhibitors in treatment of cardiovascular disease.
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Abbreviations: ACAT, acyl coenzyme A, cholesterol acyltransferase; ACE, angiotensin converting enzyme; AV, atrioventricular; BH_4, tetrahydrobiopterin; D-DES, Dexamethasone-drug eluting stents; EC, endothelial cell; GR, glucocorticoid receptor; HMGCoA, 3-Hydroxy-3-methyl-glutaryl co-enzyme A; HPA, hypothalamic pituitary adrenal; 11-HSD, 11β-hyhroxysteroid dehydrogenase; ICAM, intercellular adhesion molecule; IL, interleukin; MCP, monocyte chemotactic protein; MR, mineralocorticoid receptor; SAME, syndrome of 'apparent' mineralocorticoid excess; SLE, systemic lupus erythromatosis; TNF, tumour necrosis factor; VCAM, vascular cell adhesion molecule; (V)LDL, (very) low-density lipoprotein; VSMC, vascular smooth muscle cell; WHHL, Watanabe heritable hyperlipidaemic

Introduction

Glucocorticoids have complex, and often contradictory, influences on cardiovascular disease and cardiovascular risk (Walker, 2007a). Systemic glucocorticoid excess, caused by either increased secretion of endogenous steroid or by chronic exogenous treatment, is associated with increased cardiovascular risk. In contrast, the well-established anti-inflammatory, anti-proliferative and anti-migratory properties of glucocorticoids have led to their investigation as possible therapeutic inhibitors of atherosclerosis and restenosis following percutaneous coronary intervention (Hadoke *et al.*, 2006).

Research performed over the past 20 years has considerably improved understanding of the physiological regulation of glucocorticoid activity. Of key importance has been the demonstration that receptor activation in target tissues is not determined solely by circulating glucocorticoids but also by intra-cellular, pre-receptor inter-conversion of active and inactive forms of the steroid. This pre-receptor metabolism is catalysed by the two isozymes of 11β-hydroxysteroid dehydrogenase (11-HSD). Identification of this mechanism for local regulation of glucocorticoid action has prompted the

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concept that tissue-specific glucocorticoid excess and deficiency, in the face of normal circulating concentrations, may contribute to disease pathogenesis (Seckl and Walker, 2001). Furthermore, the presence of tissue-specific mechanisms for regulation of glucocorticoid activity suggests promising new therapeutic targets in a variety of conditions, and has prompted a drive by pharmaceutical companies to produce selective inhibitors of the 11-HSD isozymes (Webster and Pallin, 2007). There is already considerable evidence that selective inhibitors of 11-HSD1 reductase can ameliorate risk factors strongly associated with cardiovascular disease (type 2 diabetes mellitus, obesity, high blood pressure, dyslipidaemia) and this has been the subject of recent reviews (Walker, 2007a; Wamil and Seckl, 2007; Webster and Pallin, 2007). In addition to these systemic effects, it is possible that manipulation of glucocorticoid generation has direct effects in target tissues as both isozymes of 11-HSD are expressed in the heart and blood vessel wall (Walker *et al.*, 1991; Hadoke *et al.*, 2001). Indeed, recent data suggest that selective 11-HSD1 inhibition may reduce atherosclerotic lesion formation by *direct* interaction with the arterial wall (Hermanowski-Vosatka *et al.*, 2005) although the mechanisms responsible for this action remain obscure. The role of interactions between 11-HSDs, glucocorticoids and cells of the heart and vascular wall in the development of cardiovascular disease (in humans or animals) has not been clearly established. Therefore, this article will review the evidence that glucocorticoids influence cardiovascular disease by direct interaction with the heart and vascular wall and will evaluate the potential for systemic and targeted manipulation of glucocorticoid activity for the treatment of cardiovascular disease.

Glucocorticoids: systemic generation, regulation and action

Generation and metabolism

Glucocorticoids are stress hormones with a vital role in regulation of metabolic and defence responses. Their generation from cholesterol (Figure 1A), which occurs in the *zonae fasciculata* and *reticularis* of the adrenal cortex, is tightly regulated by the hypothalamic-pituitary-adrenal (HPA) axis with glucocorticoids regulating their own generation by negative feedback inhibition on several components of the axis. Under this control, glucocorticoids are produced *de novo* and released into the blood as required, with a clear circadian rhythm producing peak blood concentrations in the early morning diminishing to a nadir in the evening (Dallman *et al.*, 1993). Cortisol is the major glucocorticoid in man, whereas in rodents, which lack the enzyme 17α-hydroxylase in the adrenal, corticosterone predominates. On secretion into the blood, most (90–95%) glucocorticoids are sequestered to corticosteroid-binding globulin and albumin with only the unbound fraction available to interact with their receptors (Hammond *et al.*, 1990). Metabolic inactivation of glucocorticoids occurs predominantly in the liver, and also in the kidney, with inactive metabolites excreted in the urine. This involves a complex modification process (Figure 1B) in which glucocorticoids [and their 11-keto-metabolites (cortisone, 11-dehydrocorticosterone)] are reduced in a pathway

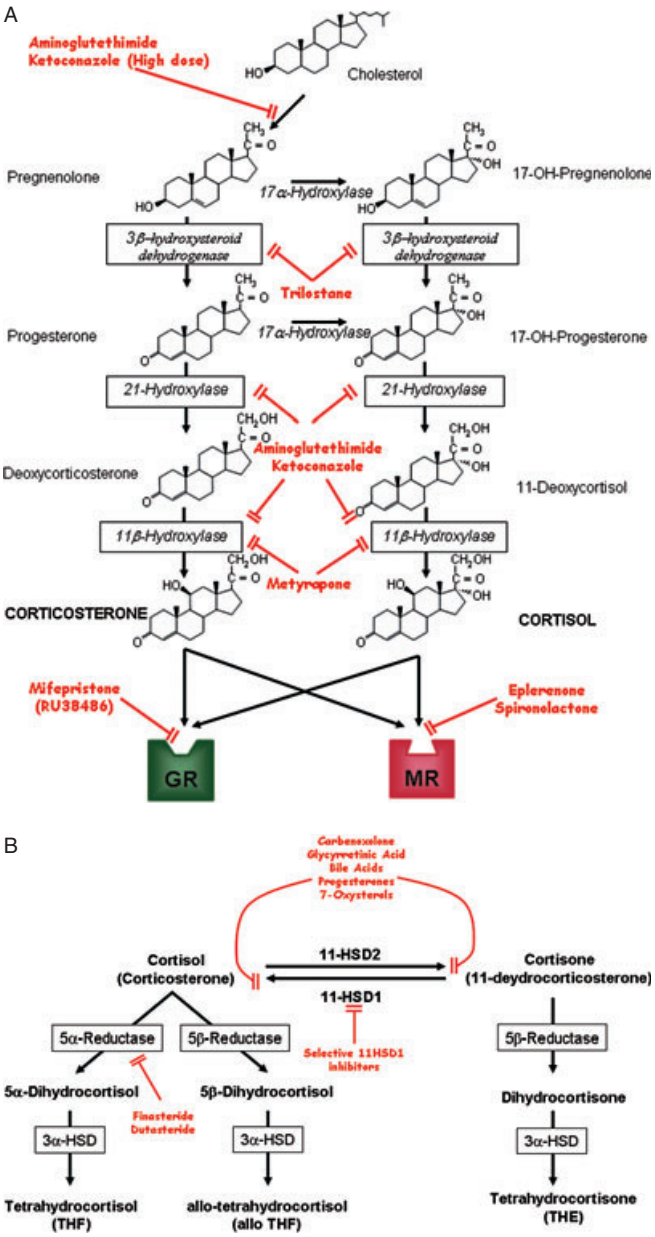

Figure 1 Strategies for pharmacological manipulation of glucocorticoid activity. (A) Therapeutic manipulation of glucocorticoid generation and action. Synthesis of active glucocorticoids (predominantly cortisol in man and corticosterone in rodents) can be targeted by inhibiting key enzymes in the pathway. Action of glucocorticoids on corticosteroid receptors can be blocked using selective antagonists of glucocorticoid (GR) and mineralocorticoid (MR) receptors. (B) Manipulation of glucocorticoid metabolism. Glucocorticoid generation in target tissues can be targeted using inhibitors of 11β-hydroxysteroid dehydrogenase (11-HSD) which interconverts active steroid and its inert 11-keto metabolite. Clearance of glucocorticoids by 5α-reductase is also inhibited by compounds used to inhibit conversion of testosterone into dihydrotestosterone.

involving 5α- and 5β-reductases, 3α-hydroxysteroid dehydrogenase, 20α- and 20β-hydroxysteroid dehydrogenases and 21-oxidase followed by conjugation with glucuronic acid or sulphates. The 11-keto metabolites are biologically inert at the glucocorticoid receptor (GR) but have been shown to attenuate the response to aldosterone (Odermatt *et al.*, 2001). In

addition, some products of glucocorticoid metabolism (e.g. 5α-terahydrocorticosterone) can activate GRs (McInnes *et al.*, 2004).

Receptor activation

Glucocorticoids are ligands both for high affinity type I [or mineralocorticoid receptors (MR)] and for low affinity type II (or GRs) corticosteroid receptors (Figure 1A) which are members of the nuclear receptor superfamily of ligand-activated transcription factors [nomenclature conforms with the BJP's guide to Receptors and Channels (Alexander *et al.*, 2008)]. These are predominantly intra-cellular receptors: although there is increasing evidence for membrane-bound versions on the cell surface (Bartholome *et al.*, 2004) their physiological relevance has not been established. GR may exist in two forms – GRα, which has a high affinity for glucocorticoids and is expressed throughout the body, and GRβ (Solakidi *et al.*, 2007) – which does not bind traditional GR agonists, acts as a dominant-negative inhibitor of GRα, is expressed in humans [but not animals (Otto *et al.*, 1997) – except perhaps the zebrafish (Schaaf *et al.*, 2008)] and has no known function *in vivo*. In contrast to GRα, MR are expressed in relatively few tissues. MR in extra-renal rat tissues bind aldosterone and corticosterone with similar affinities (Krozowski and Funder, 1983) while human MR (Kd ~1 nmol·L^{-1}) has (10–40 fold) higher affinity for cortisol than GR (Arriza *et al.*, 1987). Thus, the selectivity shown by MR for aldosterone over cortisol (which is present in the plasma in concentrations 100–1000 times higher than aldosterone) *in vivo* is largely dependent on pre-receptor metabolism of glucocorticoids by 11-HSD type 2 [(Stewart and Krozowski, 1999); see below], although other processes also have a role (Funder and Myles, 1996). Consequently, the cellular response to glucocorticoids will depend upon whether the target tissue expresses GR and/or MR and/or the isozymes of 11-HSD [discussed in (Walker, 2007b)]. Glucocorticoids bind to cytoplasmic GR after entering the cell (probably via passive diffusion), prompting dissociation of key heat shock proteins, receptor dimerization and translocation to the nucleus. Receptor dimers then bind to glucocorticoid response elements in target genes leading to alterations (induction or inhibition) in transcription which ultimately result in the appropriate physiological response. In addition, GR may interact with other factors which modify gene transcription and rapid, receptor-mediated, non-genomic actions of glucocorticoids have also been reported, resulting from initiation of signal transduction within the cytosol (Hafezi-Moghadam *et al.*, 2002).

The main actions of glucocorticoids mediated by GR stimulation are: regulation of carbohydrate and protein metabolism, negative feedback on the HPA axis, and anti-inflammatory and immunosuppressive effects. In addition, it is recognized that glucocorticoid activity also influences the cardiovascular system (Figure 2). In healthy individuals, glucocorticoids are required for blood pressure maintenance (Ullian, 1999) although the mechanisms involved are complex and incompletely understood. It is likely that several distinct interactions contribute to this activity, including regulation of: renal electrolyte and water homeostasis [by effects on glomerular filtration rate, proximal tubular epithelial sodium transport and free water clearance (Montrella-Waybill *et al.*, 1991)]; intravascular volume [by increased generation of angiotensinogen, arginine vasopressin (Raff, 1987) and atrial natriuretic peptide from the liver, hypothalamus and cardiac myocytes (Shields *et al.*, 1988), respectively]; and vascular contractility (Ullian, 1999).

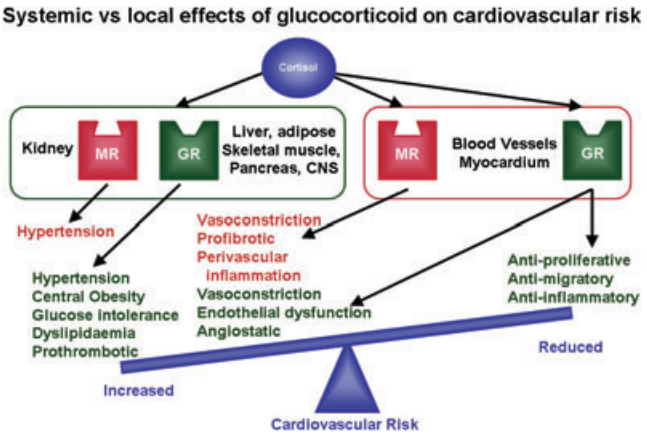

Figure 2 Systemic vs. local effects of glucocorticoids on the cardiovascular system. Systemic actions of glucocorticoids are associated with increased cardiovascular risk and are likely to promote cardiovascular disease development. Local effects on cells of the cardiovascular system may be mediated by glucocorticoid (GR) and/or mineralocorticoid (MR) receptors and could be predicted either to promote or oppose lesion development.

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

A major shift in understanding of the physiological regulation of glucocorticoid activity came with the demonstration that 11-HSD, which was originally described more than 50 years ago (Amelung *et al.*, 1953; Hubener *et al.*, 1956), did not simply provide yet another mechanism for glucocorticoid clearance. Rather, it was shown that 11-HSD activity was essential for maintaining aldosterone selectivity of MR (Edwards *et al.*, 1988; Funder *et al.*, 1988). This observation has prompted a re-evaluation of the processes regulating glucocorticoid activity and changed the concept of glucocorticoid excess (Seckl and Walker, 2001).

The isozymes of 11-HSD

Two isozymes of 11-HSD, type 1 and type 2 (Figure 1B), have now been identified, both of which are microsomal enzymes of the short-chain alcohol dehydrogenase superfamily (Stewart and Krozowski, 1999) and catalyse the interconversion of active glucocorticoids and their inert 11-keto forms (Amelung *et al.*, 1953). 11-HSD type 1 (11-HSD1) is a low affinity NADP(H)-dependent enzyme which acts predominantly as a reductase *in vivo* converting cortisone to cortisol (or 11-dehydrocorticosterone to corticosterone). Intact cells or organs [including liver (Jamieson *et al.*, 1995; 2000; Ricketts *et al.*, 1998), adipose tissue (Bujalska *et al.*, 1997), neurones (Rajan *et al.*, 1996) and vascular smooth

muscle (Hatakeyama *et al.*, 1999)] generally do not exhibit the dehydrogenase activity of this isozyme [although some tissues, such as testis, do exibit 11-HSD1 which functions as a dehydrogenase (Gao *et al.*, 1997)]. Indeed, it seems likely that early suggestions of 11-HSD1 dehydrogenase activity in vascular smooth muscle (Brem *et al.*, 1995) are attributable to 11-HSD2 (Hatakeyama *et al.*, 1999) while in other *in vitro* preparations dehydrogenase activity may be explained by release of the enzyme from damaged or dying cells (Monder and Lakshmi, 1989). The latter would result in release of 11-HSD1 from the intra-cellular environment, alteration of co-factor and substrate availability and change in redox potential: all of which may be important in driving the enzyme in the reductase direction. For example, dissociation from hexose-6-phosphate dehydrogenase may be important as this enzyme is thought to generate the high nicotinamide adenine dinucleotide phosphate (NADPH) concentrations required for reductase activity (Atanasov *et al.*, 2004). 11-HSD1, which has a Km in the $\mu mol \cdot L^{-1}$ range for both cortisol and corticosterone (Lakshmi and Monder, 1988), is widely expressed in many glucocorticoid-target tissues [including: liver, lung, adipose tissue, brain, vascular smooth muscle, skeletal muscle, anterior pituitary, gonads and adrenal cortex (Stewart and Krozowski, 1999)] where it amplifies local glucocorticoid concentrations (Seckl and Walker, 2001). Its synthesis and activity are regulated by a complex interaction of many factors, including: glucocorticoids (Hammami and Siiteri, 1991; Low *et al.*, 1994a; Takeda *et al.*, 1994), stress (Walker *et al.*, 1994; Jamieson *et al.*, 1997), sex steroids (Low *et al.*, 1994b), growth hormone (Painson *et al.*, 1992), cytokines (Cai *et al.*, 2001) and peroxisome proliferator activated receptor agonists (PPAR) (Tomlinson *et al.*, 2004).

In contrast to 11-HSD1, 11-HSD2 is a high affinity nicotinamide adenine dinucleotide dependent, exclusive dehydrogenase and converts active glucocorticoids into inactive 11-ketosteroids. It has a Km for cortisol and corticosterone in the $nmol \cdot L^{-1}$ range and is expressed constitutively, mainly in mineralocorticoid target tissues [kidney, sweat glands, salivary glands and colon (Stewart and Krozowski, 1999)] where it protects MR from illicit occupation by glucocorticoids. 11-HSD2 inhibition (using liquorice or its derivatives) [reviewed in (Walker and Edwards, 1994)], transgenic disruption in mice (Kotelevtsev *et al.*, 1999) or congenital deficiency in man (Walker *et al.*, 1992), produces the glucocorticoid-dependent syndrome of 'apparent' mineralocorticoid excess (SAME), in which inappropriate activation of MR by glucocorticoids results in characteristic sodium retention, hypokalaemia and hypertension (Walker and Edwards, 1994). It has also been noted that 11-HSD2 is expressed in tissues (such as lung, lymph nodes, heart, blood vessel wall and placenta) which are not classic MR targets (Stewart *et al.*, 1995; Slight *et al.*, 1996; Waddell *et al.*, 1998). In the placenta 11-HSD2 protects the fetus from exposure to maternal glucocorticoids (Murphy *et al.*, 1974; Brown *et al.*, 1996) while in the heart it may be important in preventing glucocorticoid-dependent, MR-mediated fibrosis (Konishi *et al.*, 2003).

Tissue-specific glucocorticoid excess/deficiency

The presence of 11-HSD-mediated pre-receptor metabolism of glucocorticoids in target tissues has highlighted the possibility of tissue-specific glucocorticoid excess (or deficiency) in the presence of normal circulating concentrations of the enzyme (Wamil and Seckl, 2007). Consequently, altered activity of 11-HSD isozymes in adipose tissue, liver, skeletal muscle and the brain have been linked to diabetes mellitus, the metabolic syndrome and cognitive dysfunction [reviewed in (Wamil and Seckl, 2007)]. The association of some of these conditions with hypertension and atherosclerosis has suggested a role for 11-HSD activity in the development of cardiovascular disease (Walker, 2007a). Whether this role is linked to regulation of systemic risk factors or to direct influence of 11-HSD activity on regulation of the cells of the heart and vascular wall has yet to be established.

Pharmacological manipulation of systemic glucocorticoid activity

Therapeutic glucocorticoid administration

Therapeutic approaches to manipulating glucocorticoids include both direct steroid administration and pharmacological manipulation of synthetic (Figure 1A) and excretory (Figure 1B) pathways. Clinically, glucocorticoid administration (often using hydrocortisone, the synthetic form of cortisol) is used predominantly to provide physiologic replacement in glucocorticoid deficiency and, in higher doses, as an anti-inflammatory (to suppress various inflammatory, allergic and autoimmune disorders) or immunosuppressant (to prevent graft rejection following transplant). The use of endogenous glucocorticoids, or their metabolites, has been supplemented by the development of synthetic compounds with greater potency, a higher degree of receptor selectivity and improved bioavailability. For example, prednisolone and methyl prednisolone have higher (3–8 fold) selectivity than cortisol for GR and have longer biological half-lives (16–40 h compared with 2–8 h for cortisol). Dexamethasone and betamethasone have even better selectivity (25–80 times) and longer biological half-lives (36–54 h). Synthetic steroids also vary in the susceptibility to metabolism by 11-HSDs for, while both prednisolone and dexamethasone are substrates for these isozymes, dexamethasone is relatively protected from dehydrogenation (Best *et al.*, 1997). It should be noted that treatments often use inactive precursor molecules (such as cortisone or prednisone) which require conversion to the active steroid. Replacement therapy, which usually uses glucocorticoids with both GR and MR activity (cortisol), is limited by their high bioavailability and short half-life (~90 min) and, consequently, cannot replicate physiological circulating concentrations (and cannot replicate the diurnal rhythm of cortisol secretion which peaks before waking). As a result, doses used tend to produce supra-physiological concentrations in the first 1–2 h after administration. In contrast to physiologic replacement, anti-inflammatory therapy tends to use GR selective compounds (such as prednisolone). The anti-angiogenic properties of glucocorticoids are also harnessed clinically in the treatment of vascular lesions such as proliferating capillary haemangiomas (Hasan *et al.*, 2000; 2003). The ubiquitous expression of GR limits the therapeutic use of glucocorticoids by mediating a variety of serious

systemic side effects (including: immunosuppression; osteoporosis; pubertal delay; central obesity; hypertension; anovulation). These can be reduced by targeting therapy (e.g. topical administration for skin conditions; inhalation for treatment of asthma). Finally, dexamethasone is also used clinically, in the dexamethasone suppression test, to assess HPA axis function (Swade *et al.*, 1987).

Pharmacological manipulation of glucocorticoid activity

In addition to therapeutic administration, pharmacological approaches have been used clinically to regulate the action of endogenous glucocorticoids. These have involved two main strategies: (i) modulation of glucocorticoid synthesis; and (ii) corticosteroid receptor antagonism (Figure 1A). Generation of glucocorticoids can be manipulated pharmacologically by inhibiting different steps in the synthetic pathway using aminoglutethimide [which inhibits 11β-hydroxylase, 17α-hydroxylase and conversion of cholesterol to pregnenalone (Brodie, 1993)]; or high dose ketoconazole [which has similar actions to aminoglutethimide and is also a GR antagonist (Sonino, 1987)]. More selective approaches include inhibition of 3β-dehydrogenase (using trilostane) or 11β-hydroxylase [metyrapone (Miller and Crapo, 1993)]. Receptor blockade can be achieved using the potent GR (and progesterone receptor) antagonist, Mifepristone [RU38486 (Spitz and Bardin, 1993); which is used primarily to induce termination of pregnancy] or the MR antagonists spironolactone and (the more selective) eplerenone (Rabasseda *et al.*, 1999). Inhibition of glucocorticoid synthesis and GR blockade have been used clinically in the treatment of Cushing's syndrome (Engelhardt and Weber, 1994) but are limited by their tendency to alter beneficial, as well as deleterious actions of glucocorticoid; leading to major side effects and compensatory changes in cortisol generation (returning cortisol to pre-treatment levels). Systemic regulation of cortisol synthesis remains a pharmacological target, however, with phase IIb trials scheduled for this year involving DiObex 2S, 4R ketoconazole (DIO-902; one of two enantiomers contained in ketoconazole) which may be safer and more effective than racemic ketoconazole (http://www.diobex.com/product902.html). Finally, glucocorticoid availability can be influenced by manipulation of steroid breakdown. For example, non-selective (dutasteride) and type 2 selective (finasteride) 5α-reductase inhibitors (Figure 1B), which are used in the treatment of benign prostatic hyperplasia and male pattern baldness (Metcalf *et al.*, 1989), may also inhibit metabolic clearance of glucocorticoids. The most significant development in this area, however, has been the recent drive to produce selective inhibitors of the 11-HSD isozymes (see below), which has considerable potential in the treatment of cardiovascular disease pathogenesis.

Influence of glucocorticoids on the cardiovascular system

For glucocorticoids to contribute to cardiovascular disease they must directly influence the function of the heart and vasculature and/or increase cardiovascular risk factors (Figure 2). Evidence that this is indeed the case is perhaps most clearly indicated by the increased cardiovascular risk factors (elevated blood pressure, central obesity, dyslipidaemia, insulin resistance) in patients with excessive production of these steroids (Cushing's syndrome). It seems likely that much of the impact of glucocorticoids on cardiovascular risk is due to interaction with the kidney, liver, adipose and central nervous system (Bjorntorp, 1991). However, while the influence of glucocorticoids on homeostasis is probably due predominantly to renal sodium retention and intravascular volume overload there is also evidence for additional, non-renal mechanisms. Notably, glucocorticoids increase peripheral vascular resistance in animals devoid of renal mass (Langford and Snavely, 1959). This is consistent with the observation that glucocorticoids can interact directly with the cells of the heart and vascular wall to alter their structure and function.

Cardiac and vascular function

Direct modulation of the heart and vasculature by glucocorticoids is, obviously, dependent on the presence of the appropriate receptors and enzymes. MR and GR are present in intact arteries (Kornel *et al.*, 1982; Christy *et al.*, 2003), cultured vascular smooth muscle (VSMC) (Meyer and Nicholls, 1981; Scott *et al.*, 1987) and endothelial (EC) (Inoue *et al.*, 1999; Jun *et al.*, 1999; Golestaneh *et al.*, 2001; Newton *et al.*, 2002; Oberleithner *et al.*, 2003) cells from several different species. Their distribution may be territory-dependent, however, as MR have been detected in rabbit aortic and pulmonary VSMCs but not in small arteries (Lombes *et al.*, 1992). Vascular GR and MR have both been shown to be active: dexamethasone-mediated induction of angiotensin converting enzyme (ACE) activity in rat aortic ECs (Sugiyama *et al.*, 2005), cortisol-mediated inhibition of prostacyclin synthesis in rat aorta (Jeremy and Dandona, 1986) and dexamethasone or cortisol-mediated increases in protein kinase C in porcine coronary artery are all sensitive to GR antagonism (Maddali *et al.*, 2005). Similarly, exposure to angiotensin II and aldosterone induces hypertrophy of VSMCs (Hatakeyama *et al.*, 1994a) and swelling of ECs (Oberleithner *et al.*, 2003) respectively. Whether membrane binding sites for corticosteroids are present, or have a role, in the vascular wall has not been established. The nature of the interaction between glucocorticoids and vascular cells may be complex as prolonged exposure *inhibits* proliferation of cultured vascular smooth muscle cells whereas short exposures (2 min-6 h) can *stimulate* a GR-dependent increase in proliferation [probably by stimulation of autocrine growth factor release (Kawai *et al.*, 1998)]. GR (Pujols *et al.*, 2002) and MR (Lombes *et al.*, 1995) are both also expressed in the myocardium, with co-expression of MR with 11-HSD2 (Konishi *et al.*, 2003) ensuring mineralocorticoid selectivity. Their relationship to cardiac function has been demonstrated by conditional GR over-expression in the heart which induces atrio-ventricular (AV) block (Sainte-Marie *et al.*, 2007). Similarly, MR knockdown induces severe heart failure and fibrosis (without hypertension or hyperaldosteronism) (Beggah *et al.*, 2002) while mice over-expressing cardiac MR develop ventricular arrhythmias (Ouvrard-Pascaud *et al.*, 2005).

The influence of glucocorticoid exposure on the heart and vascular wall is still controversial despite many reports of glucocorticoid-mediated changes in function and structure. Indeed, many early *in vitro* investigations must be discounted for using inappropriately high concentrations of steroid and short exposure times [reviewed in Walker and Williams (1992)]. In man, topical administration of glucocorticoids induces dermal vasoconstriction (Walker *et al.*, 1992) although the precise mechanism of this response remains unclear. It is widely accepted that glucocorticoid exposure potentiates contractile responses to noradrenaline and angiotensin II, although whether this is due to alterations within the VSMC or EC has not been established [reviewed in Ullian (1999) and Hadoke *et al.* (2006)]. In VSMCs glucocorticoids have been shown to up-regulate contractile receptors, alter intracellular second messenger activation and modulate the activity and synthesis of vasoactive substances leading to a direct enhancement of contraction. Increased contractility has also been attributed to changes in the endothelium but it is not clear whether this is due to: (i) increased release of endothelium-derived vasoconstrictors [such as angiotensin II or endothelin-1 (Mendelsohn *et al.*, 1982; Morin *et al.*, 1998)] and/or, (ii) impaired endothelium-dependent relaxation (Mangos *et al.*, 2000) due to impaired vasodilator (e.g. prostaglandins, nitric oxide) activity (Gerritsen and Rosenbaum, 1985; Simmons *et al.*, 1996; Wallerath *et al.*, 1999). Functional modulations of the vasculature may occur through stimulation of either GR or MR (Nagata and Hirata, 2007) as they have been reported with GR-(dexamethasone) and MR-(aldosterone) selective ligands.

In the heart, glucocorticoids may help maintain normal contractile function. Adrenalectomy results in a decreased contractile force generation in rat papillary muscles which can be prevented by treatment with dexamethasone (Lefer, 1968) which may act by modulating membrane Ca^{2+} transport (Whitehurst, Jr *et al.*, 1999; Narayanan *et al.*, 2004) and activity of K^+ channels (Lefer, 1968; Penefsky and Kahn, 1971; Wang *et al.*, 1999). Similarly, dexamethasone enhances the development of contractile tension and increases contraction and relaxation velocities in cardiac muscles (Penefsky and Kahn, 1971) although short-term administration of this compound has also been shown to decrease resting heart rate in healthy human volunteers (Brotman *et al.*, 2005). This influence of glucocorticoids on cardiac function is supported by observations from mice with over-expression of cardiac GR which have reduced heart rate and depressed cardiac conduction with AV block (Sainte-Marie *et al.*, 2007). The role of MR in regulating cardiac function is more ambiguous although recent evidence suggests MR are necessary for mediating corticosteroid-induced up-regulation of the cardiac calcium current (Rougier *et al.*, 2008).

Cardiovascular remodelling

While their ability to influence cardiovascular function is imperfectly understood, glucocorticoid-induced changes in vascular structure and growth appear more straightforward. In general glucocorticoids inhibit tube formation by endothelial cells (Nicosia and Ottinetti, 1990) and migration and proliferation of vascular smooth muscle cells (Longenecker *et al.*, 1982; 1984; Berk *et al.*, 1988); a characteristic that has been exploited in attempts to inhibit neointimal proliferation (see below). To complicate matters, however, the direct inhibition of smooth muscle cell growth may be countered by the ability of both glucocorticoids and mineralocorticoids to stimulate proliferation in these cells by potentiating the action of other hormones [see Ullian (1999)]. MR may have a role in this process as MR antagonism attenuated angiotensin II mediated hypertrophy of smooth muscle cells (Hatakeyama *et al.*, 1994b). Thus, the impact of glucocorticoids *in vivo* may reflect a balance between direct inhibition of hypertrophy, hyperplasia and migration of smooth muscle cells countered by indirect stimulation of hypertrophy and hyperplasia mediated through other factors. This process may involve both MR and GR but surprisingly few studies have directly addressed the role of these receptors in mediating corticosteroid-mediated changes in migration and proliferation of vascular smooth muscle.

The ability of glucocorticoids to alter vascular remodelling is exemplified in their inhibition of angiogenesis; a property first demonstrated by Folkman 25 years ago (Folkman *et al.*, 1983) and extended to include several steroids without classical glucocorticoid activity (Crum *et al.*, 1985; Folkman and Ingber, 1987). This work suggested that GR activation is not required for inhibition of new vessel growth but our own recent investigations have shown that corticosterone-mediated inhibition of angiogenesis in mouse aorta and subcutaneous sponge implants (Small *et al.*, 2005) is abolished by GR-receptor antagonism. The mechanism responsible for inhibition of angiogenesis has not been established, despite extensive research over many years. As inflammation plays a significant role in stimulation of angiogenesis (Risau, 1997), it is often difficult to distinguish immunosuppressive and anti-inflammatory effects of glucocorticoids from direct effects on remodelling of the vascular wall. However, the ability of glucocorticoids to inhibit the formation of tube-like structures *in vitro*, in isolation from the immune system (Nicosia and Ottinetti, 1990; Small *et al.*, 2005), suggests that direct interaction with the vascular wall does have a role. The role of glucocorticoid-mediated inhibition of angiogenesis in man has not been established and may be complex as endocrine [glucocorticoid- (Cushing's syndrome) and mineralocorticoid (primary aldosteronism)-induced] hypertension is associated with *increased* circulating levels of the pro-angiogenic vascular endothelial growth factor (Zacharieva *et al.*, 2004).

In the heart, there is evidence from experimental and human studies indicating that glucocorticoid treatment is harmful, leading to cardiomyopathy (Zecca *et al.*, 2001; Mitsuya *et al.*, 2004) characterized by an accumulation of lipid droplets, cardiomyocyte hypertrophy and dissolution of myofibrils (Clark *et al.*, 1982; de Vries *et al.*, 2002). In the adult, dexamethasone treatment can induce hypertrophy and precocious degeneration of cardiomyocytes (de Vries *et al.*, 2002) while glucocorticoid exposure in neonates can induce myocardial hypertrophy and changes in contractile proteins (Werner *et al.*, 1992; La Mear *et al.*, 1997). The mechanisms involved are not entirely understood but it has been suggested that cardiomyocyte hypertrophy up-regulates GR and MR expression and allows corticosteroid-mediated potentiation of α-adrenoceptor-mediated signalling (Lister *et al.*, 2006).

Dexamethasone also increases ACE activity (Barreto-Chaves *et al.*, 2000) which can induce myocardial fibrosis and heart failure via direct and indirect mechanisms. The role of GR in modulating cardiac remodelling is questioned, however, by the demonstration that over-expression of cardiac GR does not induce major ventricular hypertrophy or ventricular arrhythmias (Sainte-Marie *et al.*, 2007). MR activation, in contrast, is clearly associated with cardiac remodelling. Mineralocorticoids have potent pro-fibrotic effects, *in vitro* (Neumann *et al.*, 2002; Stockand and Meszaros, 2003) and *in vivo* (Brilla *et al.*, 1990a; 1993), and can promote oxidative stress (Sun *et al.*, 2002). Aldosterone can also amplify the action of angiotensin II by increasing AT_1 receptor density (Robert *et al.*, 1999) and ACE activity (Harada *et al.*, 2001) leading to cardiac fibrosis (Brilla *et al.*, 1990b; McEwan *et al.*, 1998; Ramires *et al.*, 1998; Lijnen and Petrov, 2000; Lijnen *et al.*, 2000). Blockade of MR (eplerenone) attenuates ventricular hypertrophy, ventricular fibrosis, myocardial stiffening and relaxation abnormalities (Ohtani *et al.*, 2007) while clinical studies report beneficial effects of MR antagonists on mortality in heart failure patients (Pitt *et al.*, 1999; 2003). In addition, mice with over-expression of cardiac MR die in the embryonic and perinatal period secondary to severe ventricular arrhythmia without high-degree AV block (Ouvrard-Pascaud *et al.*, 2005).

In addition to direct modulation of remodelling by cardiac and vascular cells, glucocorticoids may also alter structural changes in the cardiovascular system by regulating the inflammatory response to injury. It is becoming apparent, however, that the model of glucocorticoids as inhibitors of inflammation may be simplistic as, depending on circumstances [including glucocorticoid concentration (Lim *et al.*, 2007)], they may inhibit *or* stimulate the inflammatory response [reviewed in Yeager *et al.* (2004)]. Much of this anti-inflammatory activity may be due to direct interaction with inflammatory cells. Glucocorticoids can influence a variety of GR-dependent functions of macrophages, lymphocytes, eosinophils and neutrophils (Heasman *et al.*, 2003), including apoptosis, phagocytosis, adhesion molecule expression and expression of inflammatory genes [reviewed in Valledor and Ricote (2004)]. For example, glucocorticoids inhibit up-regulation of adhesion molecules on lymphocytes by stimulation of GR (blocked by RU38486) and also by non-genomic mechanisms [reviewed in Pitzalis *et al.* (2002)]. In macrophages both GR and MR are expressed but the action of glucocorticoids on these cells appears to be solely dependent on GR stimulation (Lim *et al.*, 2007). In addition, GR- (Wheller and Perretti, 1997) and MR- (Caprio *et al.*, 2008) dependent mechanisms also regulate induction of adhesion molecules in the vascular endothelium and, thus, suppress passage of neutrophils into the vessel wall. The role of these interactions is discussed further in relation to cardiovascular disease (below).

Finally, glucocorticoids may also influence the cardiovascular system by modulating coagulation of the blood both by direct modulation of clotting factors and by inhibition of anti-thrombotic pathways in the endothelium (Yamamoto *et al.*, 2004). *In vitro* evidence suggests that glucocorticoids may activate haemostasis and inhibit thrombolysis, thereby increasing the likelihood of clot formation. Whether this is significant *in vivo* may depend on dose and duration of treatment (Brotman *et al.*, 2006).

Prenatal programming of the cardiovascular system

A more esoteric mechanism through which glucocorticoids may alter the function and structure of the cardiovascular system is the process of prenatal 'programming'. This is based on the increasing evidence that exposure to glucocorticoid excess *in utero* can induce low birth weight and programme the development of increased cardiovascular risk in later life (Seckl and Meaney, 2004). Experimental fetal exposure to excess maternal glucocorticoid (by direct administration or by inhibition of placental 11-HSD2) leads to reduced birth weight (Benediktsson *et al.*, 1993) which is associated with increased risk of cardiovascular and metabolic disease in adulthood (Barker *et al.*, 1990). Indeed, maternal dietary restriction and maternal stress, both major causes of low birth weight, may act by modulation of glucocorticoid activity (Woodall *et al.*, 1996; Lesage *et al.*, 2001). Whether development of cardiovascular risk factors, such as hypertension, in adulthood (Dodic *et al.*, 1998) is due to programmed changes in the vasculature itself has not been established but may be related to the ability of glucocorticoids to increase blood pressure and alter vascular function in the fetus (Gao *et al.*, 1996). However, although altered vascular structure and enhanced contractility are evident in rats (Lamireau *et al.*, 2002; Khan *et al.*, 2005) and sheep (Roghair *et al.*, 2005) with programmed hypertension [as is left ventricular hypertrophy and reduced cardiac functional reserve (Dodic *et al.*, 2001)], it is not clear whether this contributes to (or is a consequence of) elevated blood pressure.

Cardiovascular 11-HSDs

Whatever the influence of glucocorticoids on the heart and vascular wall, these interactions are liable to modification by pre-receptor metabolism as both isozymes of 11-HSD are expressed in cardiac (Walker *et al.*, 1991; Lombes *et al.*, 1995; Slight *et al.*, 1996) and vascular cells (Ullian, 1999; Alzamora *et al.*, 2000). Evidence suggests that 11-HSD2 may be the predominant isozyme in cardiac cells (Slight *et al.*, 1996) whereas 11-HSD1 is the most active isozyme in the arterial wall (Figure 3; Walker *et al.*, 1991; Christy *et al.*, 2003). The cellular localization of 11-HSD isozymes in cardiovascular tissues is not clear. There are several reports of both enzymes in the VSMC (Hatakeyama *et al.*, 1999; Cai *et al.*, 2001) and also in the EC (Brem *et al.*, 1998): our own studies have suggested that (in the mouse and rat aorta) 11-HSD2 is localized to ECs whereas 11-HSD1 is predominantly in the VSMC (Walker *et al.*, 1991; Christy *et al.*, 2003). It is often difficult to compare studies, however, as there is variation in arteries studied (species, anatomical origin) and analytical techniques employed [e.g. in contrast to our work in intact arteries, 11-HSD2 activity was not detected in human umbilical vein ECs (Schleimer, 1991)]. This is significant as the cellular distribution of 11-HSDs differs between vascular territories and 11-HSD activity may increase as arterial diameter decreases (Walker *et al.*, 1991). Interpretation of studies performed in culture is also difficult as the expression and activity of

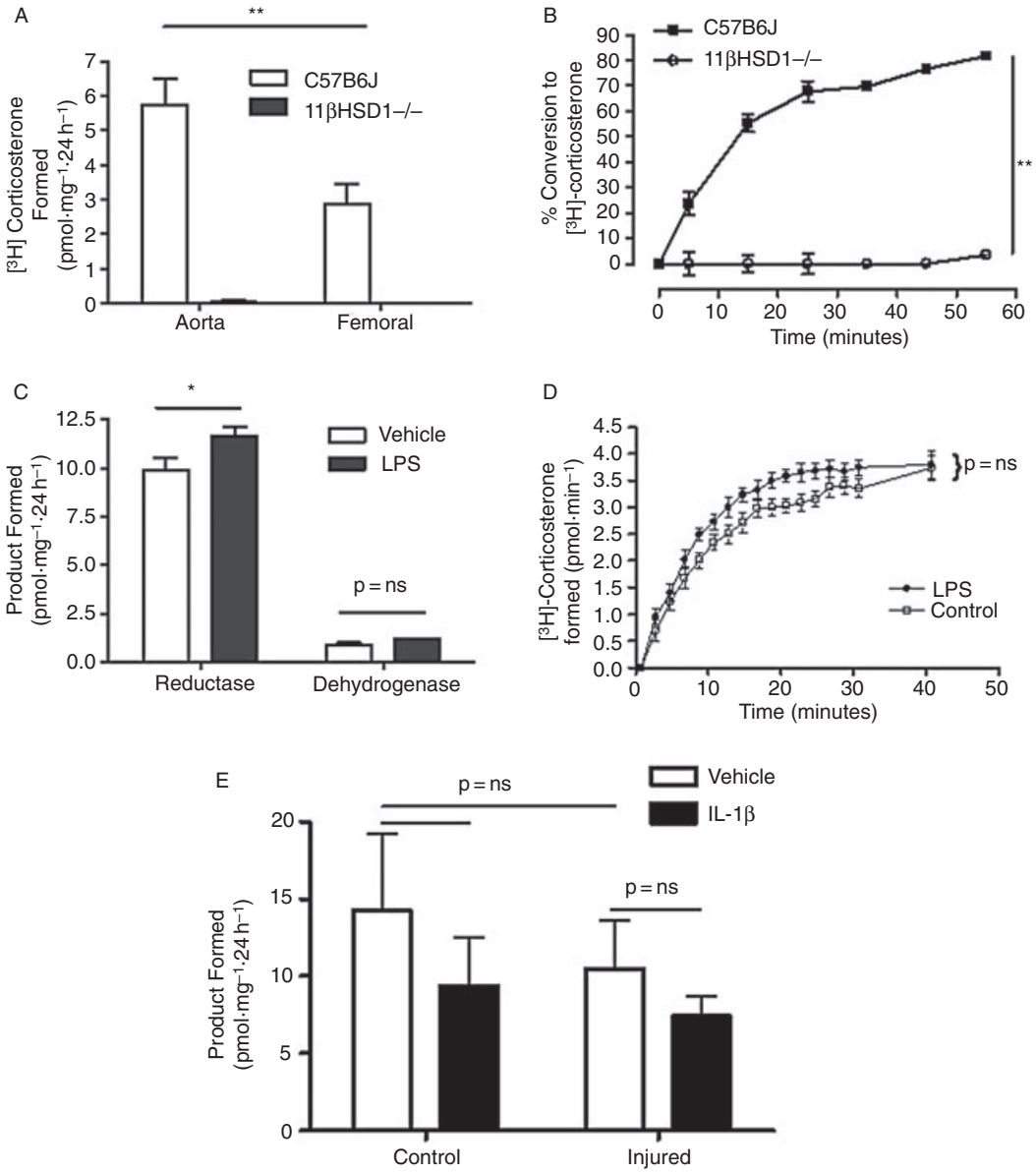

Figure 3 The influence of inflammation on 11β-hydroxysteroid dehydrogenase activity in murine arteries. Glucocorticoid generation in (A) isolated mouse aorta and femoral artery and (B) perfused mouse hindlimb is catalysed exclusively by 11-HSD1 type 1 as deletion of this isozyme completely prevents generation of corticosterone. Exposure of mice to a pro-inflammatory stimulus [lipopolysaccharide (LPS), 6 h] produced a small increase in reductase activity that achieved significance in isolated arteries (C) but not in the perfused hindlimb (D). Similarly, induction of an inflammatory response to intravascular injury in the mouse femoral artery (E) did not increase 11-HSD1 reductase activity in either the presence or absence of pro-inflammatory cytokines (Interleukin 1β; IL-1β) *in vitro*. Adapted with permission from Dover *et al.*, 2007 *Endocrinology*, 148, 166–172.

11-HSDs appears to be regulated by cell proliferation and passage number (Dover *et al.*, 2007). Despite these uncertainties, it is becoming increasingly evident that 11-HSD activity is an important determinant of glucocorticoid-mediated modulation of vascular function, structure, growth and inflammation.

The influence of 11-HSD activity on vascular structure has been addressed using mice with selective 11-HSD isozyme deletion. No evidence has been found for altered cardiovascular structure in 11-HSD1$^{-/-}$ mice (Kotelevtsev *et al.*, 1997) but 11-HSD2 deletion results in cardiac hypertrophy and occasional aortic rupture (particularly in pregnant females) (Kotelevtsev *et al.*, 1999). However, as with determining the effects of glucocorticoids on cardiovascular structure, it is difficult to establish the direct effects of 11-HSD deletion from secondary effects mediated by changes in blood pressure. The role of 11-HSDs in regulating angiogenesis can, however, be addressed directly using isolated vascular rings (Small *et al.*, 2005). Work by our own group has shown that 11-HSD1 in the vascular wall regulates angiogenesis by generation of active glucocorticoids from their 11-keto forms (Small *et al.*, 2005). Similar results were obtained in a model of *in vivo* angiogenesis although this effect may be influenced by alterations in inflammatory response.

More recently, 11-HSD activity has been described in inflammatory cells from mice (macrophages, lymphocytes) and humans (macrophages, neutrophils). In both species, 11-HSD activity in these cells appears to be exclusively reductase activity of the type 1 isozyme (Thieringer *et al.*, 2001; Zhang *et al.*, 2005a; Ishii *et al.*, 2007; Kardon *et al.*, 2008). 11-HSD1 expression is induced on cellular differentiation: for example from monocytes to macrophages (Thieringer *et al.*, 2001), and in polarization of lymphocytes into Th1 or Th2 cells (Zhang *et al.*, 2005a). In addition, 11-HSD1 activity in inflammatory cells is increased by exposure to pro-inflammatory cytokines (Thieringer *et al.*, 2001; Zhang *et al.*, 2005a) and regulates both GR activation (Zhang *et al.*, 2005a) and cellular function [such as neutrophil apoptosis (Kardon *et al.*, 2008) and phagocytosis of apoptotic neutrophils by macrophages (Gilmour *et al.*, 2006)]. These data clearly suggest, therefore, that 11-HSD1 activity in inflammatory cells has a role in regulating the inflammatory response (Chapman *et al.*, 2006).

Glucocorticoids and cardiovascular pathophysiology

The link between glucocorticoids and cardiovascular disease has been evident since the work of Adlersberg and colleagues in the 1950s suggesting that the impact of cortisone treatment on serum lipids might cause premature atherosclerosis (Adlersberg *et al.*, 1950a,b,c). Pathological evidence associating elevated cortisol with atherosclerosis emerged in the same decade (Etheridge and Hochligeti, 1952). It is evident that glucocorticoids have the potential to regulate the cardiovascular system both indirectly, by systemic modulation of risk factors [hypertension and obesity; see Walker *et al.* (1998)], and directly by interaction with cells of the heart and vascular wall. Most of the indirect systemic effects of glucocorticoids lead to an increase in cardiovascular risk factors and, therefore, are linked to the prognosis of increased cardiovascular events (Dallman *et al.*, 1993; Andrews and Walker, 1999; Walker, 2007b). In contrast, direct interaction of glucocorticoids with cardiovascular cells can induce changes that could variously promote or inhibit development of cardiovascular disease and it is not clear which predominate (Figure 2). Since they induce profound inhibition of inflammation, proliferation and migration, it seems logical that, in the absence of systemic effects, glucocorticoid administration would inhibit the remodelling processes that lead to lesion formation in atherosclerosis, restenosis and chronic graft rejection. In addition, glucocorticoid-mediated regulation of inflammation and angiogenesis may have a beneficial impact on myocardial remodelling following ischaemia. With the demonstration that MR activation can have a profound influence cardiovascular disease development [reviewed in Young (2008)], it is becoming increasingly evident that, in addition to their classical actions on GR, stimulation of MR by glucocorticoids may also have a significant role in these disease pathophysiology.

The major remodelling processes associated with cardiovascular disease all have their basis in the process of wound healing in response to injury. Atherosclerosis is widely accepted to be the result of an unfettered inflammatory response to chronic insult (Ross, 1999; Libby *et al.*, 2002), while restenosis following revascularization is mediated predominantly by inflammation, combined with proliferation and migration of VSMCs, in response to acute injury (Wainwright *et al.*, 2001). Similarly, chronic graft rejection is caused by a progressive thickening of the vascular wall associated with inflammation and EC dysfunction (Brazelton *et al.*, 1999) while, in the heart, myocardial ischaemia prompts a wound healing response characterized by inflammation, angiogenesis and fibrosis (Michael *et al.*, 1999). In atherosclerosis, symptoms are caused by the interruption of blood supply to vulnerable tissues as a result either of a progressive increase in lesion size or, more significantly, of rupture and thrombosis of vulnerable lesions (Weissberg, 2000). The ability of HMGCoA reductase inhibitors ('statins') to reduce cardiovascular events without appreciable changes in lesion size has been attributed to increased plaque stability (Son *et al.*, 2003). This has important implications for anti-atherosclerotic interventions as agents that inhibit VSMC proliferation might inhibit development of restenotic lesions but, by degrading the protective fibrous cap, increase the vulnerability of atheroma.

Based on our understanding of cardiovascular remodelling processes, the direct action of glucocorticoids could be predicted to increase or decrease risk, depending on disease pathology and on which action predominates (Figure 2). Inhibition of inflammation, in the heart and in the vasculature (and by actions on circulating inflammatory cells) would be expected to inhibit the development of fibro-fatty lesions in atherosclerosis, remove the stimulus for VSMC migration and proliferation in restenosis (Miller *et al.*, 2001; Wainwright *et al.*, 2001) and graft rejection and also attenuate scarring and fibrosis in the healing myocardium. However, the influence of glucocorticoids on adhesion molecules, which mediate the inflammatory response, is complex. In healthy men, for example, dexamethasone inhibits circulating E-selectin and intercellular adhesion molecule (ICAM)-1 (Jilma *et al.*, 2000) but, while glucocorticoids inhibit NFκB – induced endothelial vascular cell adhesion molecule (VCAM)-1 expression, they also stabilize VCAM-1 mRNA (Simoncini *et al.*, 2000). Similarly, in restenosis/graft rejection, glucocorticoid-mediated inhibition of VSMC migration (Goncharova *et al.*, 2003) and proliferation (Longenecker *et al.*, 1982; 1984), plus their ability to inhibit thrombin-induced expression of growth factors [platelet-derived growth factor A chain and heparin binding epidermal growth factor like growth factors] by VSMCs (Nakano *et al.*, 1993), would be predicted to be beneficial, reducing neointimal lesion formation. In contrast to these beneficial effects, however, inhibition of these processes, combined with stimulation of glucocorticoid-induced tumour necrosis factor (TNF) receptor family-related protein-mediated activation of macrophages (Kim *et al.*, 2006b), is likely to contribute to destabilization of atherosclerotic lesions. Glucocorticoids may also exacerbate the consequences of lesion rupture by modulating factors involved in coagulation and fibrinolysis (clotting factors and fibrinogen) to produce a prothrombotic state (Brotman *et al.*, 2006). Other processes may also favour lesion development, including: glucocorticoid-mediated inhibition of endothelial

nitric oxide generation [possibly by production of superoxide (Iuchi *et al*., 2003) or inhibition of tetrahydrobiopterin (BH_4) generation (Johns *et al*., 2001)], leading to increased VSMC proliferation and migration (Radomski *et al*., 1990); stimulation of ACE activity (Mendelsohn *et al*., 1982; Fishel *et al*., 1995) contributing to increased VSMC proliferation [since ACE inhibition limits neointimal proliferation following balloon injury (Powell *et al*., 1989; Capron *et al*., 1991)]; stimulating release of the vasoconstrictor and growth factor, endothelin-1 (Kato *et al*., 1995); increasing vasoconstriction leading to reduced vascular lumen diameter (Ullian, 1999); impairment of cholesterol removal from the arterial wall [by stimulating cholesteryl ester formation in smooth muscle cells (Petrichenko *et al*., 1997)]; and, increasing vascular calcification [due to promotion of osteoblastic differentiation of VSMCs (Mori *et al*., 1999)]. Finally, some studies from the 1970s and 1980s suggested that inhibition of inflammation and VSMC proliferation and atherosclerotic plaque formation (possibly by inhibition of heat shock proteins) in the heart is likely to be beneficial following infarction (Alisky, 2006). These effects may be counter-balanced, however, by a detrimental inhibition of angiogenesis during wound healing (Small *et al*., 2005).

In the context of inflammatory cardiovascular remodelling, the direct interaction of glucocorticoids with inflammatory cells may have an influence on the wound healing response. For example, dexamethasone inhibits interleukin-6 (IL-6) release (Wirtz *et al*., 2004a), but stimulates TNF-α secretion (Wirtz *et al*., 2004b), from monocytes. These processes may be linked [since dexamethasone-mediated inhibition of IL-6 production is blocked in the presence of high TNF-α (Wirtz *et al*., 2004a)] and may also be influenced by systemic risk factors [as dexamethasone-induced TNF-α release is increased in monocytes from patients with essential hypertension (Wirtz *et al*., 2004b)]. Given the role of macrophages in the formation of atherosclerotic and neointimal lesions, the ability of glucocorticoids to increase phagocytic activity (McColl *et al*., 2007), inhibit scavenger receptor activity (Roberts *et al*., 1998) and inhibit endothelin-1-mediated release of TNF-α from these cells (Ruetten and Thiemermann, 1997) may be important. In addition, glucocorticoids may promote foam cell formation by increasing the accumulation of cholesterol esters, by enhancing acyl coenzyme A: cholesterol acyltransferase 1 (ACAT-1) expression (Yang *et al*., 2004). The ability of glucocorticoids to influence inflammatory cells is not limited to monocyte/macrophage/foam cells as dexamethasone can also attenuate serum amyloid-A-induced release of TNF-α from neutrophils (Hatanaka *et al*., 2004).

Pathophysiological role of cardiovascular 11-HSDs

Positive and negative effects of glucocorticoids on the heart, blood vessel wall and inflammatory response are likely to be modulated by pre-receptor metabolism in cells containing 11-HSD1 and/or 11-HSD2. Indeed, a key role of these enzymes may be to regulate access of glucocorticoids to MR in the heart and vasculature (Molnar *et al*., 2008). The induction of 11-HSD1 activity in monocytes as they differentiate into macrophages (Thieringer *et al*., 2001) suggests a mechanism for amplification of phagocytosis (McColl *et al*., 2007) and, hence, accelerated resolution of inflammation. Perhaps more striking is the demonstration that pro-inflammatory cytokines up-regulate 11-HSD1, but down-regulate 11-HSD2, in human smooth muscle cells, thereby favouring the generation of active glucocorticoid (Cai *et al*., 2001). This suggests a mechanism for local feedback regulation of inflammation in the vascular wall which would be expected to protect against the excessive inflammatory response central to atherogenesis. In our own studies (Dover *et al*., 2007) with intact murine arteries, however, *in vitro* exposure to various inflammatory stimuli or *in vivo* exposure to lipopolysaccharide had no effect on (or produced only small increases in) 11-HSD1 reducatse activity (Figure 3C,D). In addition, our work in mice (Small *et al*., 2005) indicates that 11-HSD isozymes regulate the angiogenic growth of blood vessels. This may influence both cardiac remodelling and atherogenesis in which angiogenesis provides an important mechanism for supplying oxygen to vascular and cardiac cells.

Glucocorticoid-mediated regulation of atherosclerosis

The various actions of glucocorticoids on the heart, vascular wall and inflammatory cells, combined with their ability to influence cardiovascular risk factors, make it difficult to predict their effect on cardiovascular disease *in vivo*. Endogenous glucocorticoid excess in humans appears to be predictive of cardiovascular morbidity and mortality (Colao *et al*., 1999): predominantly epidemiological studies have shown correlation of endogenous plasma corticosteroid levels with disease severity (Table 1). Retrospective analysis of the association between plasma cortisol concentrations and atherosclerosis demonstrated a significant correlation of elevated morning plasma cortisol levels with angiographically determined moderate-to-severe coronary atherosclerosis (Troxler *et al*., 1977) and an increase, independent of age or sex, in the number of coronary vessels with severe stenosis (Alevizaki *et al*., 2007). These results are consistent with studies of endogenous corticosteroid excess which can be caused by a variety of conditions (e.g. Cushing's syndrome, primary hyperaldosteronism, renal artery stenosis). For example, patients with untreated or non-remitting Cushing's disease exhibit a fourfold increase in mortality, compared with the general population, mainly as a result of vascular disease (Etxabe and Vazquez, 1994) while the combination of chronic HPA axis hyper-reactivity with tissue hypersensitivity to glucocorticoids has been linked to more severe atherosclerosis (Alevizaki *et al*., 2007). This is supported by the demonstration that normalization of glucocorticoid levels in patients with Cushing's disease improves a variety of vascular parameters, including: the distensibility coefficient, systolic lumen diameter and intima-media thickness (Faggiano *et al*., 2003). In addition to Cushing's syndrome, congenital adrenal hyperplasia (due to 21-hydroxylase deficiency) which causes a tendency to obesity, high insulin and hypertension in children and adolescents, is linked with increased intima-media thickness in the aorta and other major conduit arteries (common carotid A, carotid bulb, femoral A) (Sartorato *et al*., 2007). It has also been proposed that aggressive treatment to lower low-density lipoprotein (LDL) levels in atherosclerosis may affect the synthesis of steroid hormones (Kanat *et al*., 2007).

Table 1 The relationship between glucocorticoid excess and atherosclerosis in human studies

Patient group	*Design and intervention*	*Outcome*	*Reference*
Endogenous glucocorticoid excess			
Cushing's syndrome	Epidemiological study	Increased mortality (4×)	(Etxabe and Vazquez, 1994)
	Normalization of cortisol levels	Improved vascular parameters	(Faggiano *et al.*, 2003)
	Normalization of cortisol levels	Cardiovascular risk remains elevated	(Colao *et al.*, 1999)
CAH	Ultrasound analysis	Increased intima/media thickness	(Sartorato *et al.*, 2007)
Requiring angiography	Elective cortisol measurement	Increased cortisol correlated with increased atherosclerosis	(Troxler *et al.*, 1977), (Alevizaki *et al.*, 2007)
Chronic glucocorticoid administration			
Glucocorticoid users	Cohort study	Increased risk of cardiovascular events	(Wei *et al.*, 2004)
	Cohort study	Increased risk of heart failure	(Souverein *et al.*, 2004)
	Cohort study	Increased risk of acute myocardial infarction	(Varas-Lorenzo *et al.*, 2007)
Rheumatoid arthritis	Cohort study	Increased cardiovascular mortality	(Sihvonen *et al.*, 2006)
	Cohort study	Increased risk of cardiovascular events	(Davis *et al.*, 2007)
	Cohort study	Increased risk of cardiovascular events	(Solomon *et al.*, 2006)
	Cohort study	Increased carotid artery plaque and arterial stiffness	(del Rincon *et al.*, 2004)
	Cohort study	Increased cholesterol but no effect on atherosclerosis or EC function	(Hafstrom *et al.*, 2007)
Polymyalgia rheumatica	Cohort study	No increase in cardiovascular events	(Kremers *et al.*, 2007)
Giant cell arteritis	Cohort study	No increase in atherosclerosis	(Gonzales-Juanatey *et al.*, 2007)
	Cohort study	Increased blood pressure	(Fardet *et al.*, 2007)
SLE	Cohort study	Increased carotid and femoral lesions	(Vlachoyiannopoulos *et al.*, 2003)

CAH, congenital adrenal hyperplasia; EC, endothelial cell; SLE, systemic lupus erythromatosis.

When evaluating these studies, however, it should be noted that, given the diurnal fluctuations in secretion and the importance of tissue-specific regulation, simple measurement of steroid concentrations in biological fluids (such as blood, saliva and urine) will give only a very crude indication of glucocorticoid activity.

Exogenous glucocorticoid therapy is also associated with cardiovascular disease, as judged by assessment of the effect on cardiovascular risk factors in patients receiving glucocorticoid replacement, and by pharmacoepidemiological investigations of patients receiving chronic administration of anti-inflammatory doses of glucocorticoid for treatment of disease (e.g. Lupus, rheumatoid arthritis) (Table 1). This increased risk is cumulative and dose-dependent, is mainly observed during the first month of treatment (Wei *et al.*, 2004; Davis *et al.*, 2007) and is reduced if treatment is discontinued (Souverein *et al.*, 2004; Varas-Lorenzo *et al.*, 2007). Daily administration of prednisolone in dose equivalents exceeding 10 mg, for example, was associated with a twofold increased risk of acute myocardial infarction (Varas-Lorenzo *et al.*, 2007). The relationship between chronic glucocorticoid therapy and cardiovascular disease has been addressed most consistently in patients with progressive inflammatory conditions, such as rheumatoid arthritis and systemic lupus erythromatosis (SLE). In rheumatoid arthritis the risk of mortality (predominantly from cardiovascular disease) increases by 14% after 1 year, rising to 69% after 10 years, in patients treated with low-dose, oral glucocorticoids (Sihvonen *et al.*, 2006). These outcomes are consistent with detection of increased risk of cardiovascular risk in similar groups of patients (del Rincon *et al.*, 2004; Solomon *et al.*, 2006; Davis *et al.*, 2007) and have been associated with carotid plaque and arterial distensibility independent of cardiovascular risk factors and clinical manifestations (del Rincon *et al.*, 2004). It should be noted, however, that, in one study, oral low-dose prednisolone had no effect on endothelial cell function, atherosclerosis or atherosclerotic risk factors in a cohort of patients with rheumatoid arthritis (Hafstrom *et al.*, 2007). Chronic glucocorticoid administration also increased cardiovascular risk in patients with SLE (Vlachoyiannopoulos *et al.*, 2003; Fischer-Betz *et al.*, 2005). Of some concern is a recent study on patients with SLE which suggested that glucocorticoid administration decreased the effectiveness of the anti-atherosclerotic drug pravastatin (Costenbader *et al.*, 2007). This pro-atheromatous effect of glucocorticoids seems most likely to be caused by increasing systemic risk factors (e.g. hypertension) and, indeed, has been linked to: increased cholesterol levels [in patients with SLE (Sarkissian *et al.*, 2006; 2007); impaired metabolism of atheroprotective high density lipoproteins (Beentjes *et al.*, 2000); and increased insulin resistance following transplant (Armstrong *et al.*, 2005; Oterdoom *et al.*, 2007)]. Impaired EC function (flow-mediated dilatation) in SLE could not, however, be attributed to the cumulative dose of prednisolone (Lima *et al.*, 2002). A limitation of these studies is that it is difficult to differentiate the effect of treatment from that of the underlying inflammatory condition, a factor which may contribute to investigations in patients with different forms of inflammatory disease (e.g. polymyalgia rheumatica) that found no association between glucocorticoid therapy and cardiovascular risk.

In addition to these associations between glucocorticoid excess and systemic risk factors, there is some data to suggest that the interaction of glucocorticoids with the vascular wall is impaired in cardiovascular disease. This mainly revolves around alteration of arterial GR activity with GR expression, which is high in the media of human carotid arteries, reduced in cells from human vascular lesions (Bray *et al.*, 1999). This may be a consequence of increased lipid deposition as both

Table 2 The influence of endogenous glucocorticoid excess or glucocorticoid treatment on atherosclerosis in animal models

Sample	*Design and intervention*	*Outcome*	*Reference*
Monkey (stress)	Depression; impaired HPA feedback	No effect on atherosclerosis	(Shively *et al.*, 2002)
Pigeon	Dexamethasone	Reduced abnormalities in aortic ECs	(Deitemeyer *et al.*, 1985)
Cockerel (fat-fed),	Cortisone (1–15 mg·day^{-1})	Moderate increase in aortic and coronary atherogenesis	(Stamler *et al.*, 1954)
	Hydrocortisone (1–2 mg·day^{-1})	No effect on aortic or coronary atherogenesis	(Stamler *et al.*, 1954)
	Hydrocortisone (1 mg·day^{-1})	Reduced coronary atheroma	(Jain *et al.*, 1965)
Rabbit (fat-fed)	Cortisone (10 mg 3× week^{-1})	Reduced lesion development	(Oppenheim and Bruger, 1952)
	Cortisone (5 mg·day^{-1})	No effect on atherosclerosis	(Ashton and Cook, 1952)
	Cortisone (1–3 mg·kg^{-1})	Reduced aortic lesion development	(Gordon *et al.*, 1954)
	Cortisone	Reduced arterial lipid deposition	(Stumpf and Wilens, 1954)
	Prednisolone		(Constantinides *et al.*, 1962)
	Cortisol	Reduced proliferation in lesions	(Cavallero *et al.*, 1976)
	Cortisone 5–10 mg	Reduction in lesion formation	(Bailey and Butler, 1985)
	Dex (125 mg·day^{-1})	Reduced lesion development	(Naito *et al.*, 1992)
	Dex (125 mg·day^{-1})	Reduced lesion development	(Asai *et al.*, 1993)
Rabbit (WHHL)	Cortisone (5 mg·day^{-1})	60% reduction in atherogenesis	(Makheja *et al.*, 1989)
	Social stress	Increased lesion formation and severity	(Mccabe *et al.*, 2002)

EC, endothelial cell; Dex, dexamethasone; HPA, hypothalamic-pituitary adrenal axis; WHHL, Watanabe heritable hyperlipidaemic.

LDL and VLDL can inhibit glucocorticoid binding by reducing the number of GR in human cells (Shakhov *et al.*, 1989; 1993).

The effects of elevated glucocorticoids on atherosclerosis in animal models contrast strikingly with their adverse effects in clinical investigations (Table 2). Glucocorticoids, and other anti-inflammatory steroids, prevent or arrest atherosclerosis in fat-fed rabbits, despite increasing hyperlipidaemia (Jain *et al.*, 1965; Bailey and Butler, 1985; Naito *et al.*, 1992; Asai *et al.*, 1993). This effect was first demonstrated over 50 years ago (Oppenheim and Bruger, 1952; Gordon *et al.*, 1954; Stumpf and Wilens, 1954; Constantinides *et al.*, 1962) and has subsequently proved to be reproducible in this model (Cavallero *et al.*, 1976; Bailey and Butler, 1985; Naito *et al.*, 1992; Asai *et al.*, 1993) and in rabbits with inherited hypercholesterolaemia [Watanabe heritable hyperlipidaemic (WHHL); Makheja *et al.*, 1989]. There is also an indication that social stress, which increases cortisol and corticosterone secretion in New Zealand white and WHHL rabbits (Szeto *et al.*, 2004) increases atherogenesis in the latter (Mccabe *et al.*, 2002). In female cynomologus monkeys, however, while depression increased sensitivity to negative feedback regulation of the HPA axis, it had no effect on atherogenesis or vascular function after prolonged exposure to a high-fat diet (Shively *et al.*, 2002). A single study in atherosclerosis-susceptible pigeons suggested that glucocorticoid administration in early life influences aortic prostaglandin synthesis and morphology (Deitemeyer *et al.*, 1985). In cockerels, cortisone has been shown to both increase (Stamler *et al.*, 1954) and reduce atheroma (Jain *et al.*, 1965) (while cortisol had no effect). There is insufficient information to determine the reason for these contradictions.

The mechanism(s) underlying this anti-atherosclerotic effect of glucocorticoids is (are) incompletely understood. Suggestions include: inhibition of DNA synthesis in the cellular component of lesions (in fat-fed rabbits; Cavallero *et al.*, 1976); inhibition of inflammatory cell proliferation (Asai *et al.*, 1993); inhibition of intimal VSMC proliferation (Voisard *et al.*, 1994) and migration (Van Put *et al.*, 1995); reduced chemotaxis of circulating monocytes and macrophages into the sub-endothelial space (Prescott *et al.*, 1989; Yamada *et al.*, 1993); inhibition of macrophage proliferation by GR-mediated-attenuation of oxidized-LDL-induced granulocyte/macrophage colony-stimulating factor production by (human and murine) inflammatory cells (Sakai *et al.*, 1999); GR-mediated reduction of reactive oxygen species generation in (human) aortic VSMCs (Marumo *et al.*, 1998); and GR-mediated inhibition of monocyte chemotactic protein (MCP)-1 (the dominant mediator of macrophage accumulation in atherosclerotic plaques) secretion by marked reduction in MCP-1 mRNA stability (Fasshauer *et al.*, 2004; Dhawan *et al.*, 2007). Whatever the mechanism(s) responsible for glucocorticoid-mediated inhibition of atherosclerosis in animal models, one of the most important questions has not been answered: why do these steroids apparently inhibit lesion development in animals but increase it in humans?

The ability of 11-HSD activity to influence atherosclerosis, presumably by regulating glucocorticoid generation in key metabolic and cardiovascular tissues, has been demonstrated in a small number of studies in which 11-HSD inhibitors were administered to dyslipidaemic mice (see below). However, while 11-HSD activity in inflammatory cells, cardiac myocytes, VSMCs and ECs (in animals and in man) suggests it has a role in regulating the inflammatory response to injury, there is little evidence that this is important in regulating cardiovascular disease.

Glucocorticoid-mediated regulation of neointimal proliferation

Several properties of glucocorticoids suggest that they may prevent the intense fibro-proliferative vascular remodelling that occurs following percutaneous revascularization (angioplasty, stenting), prompting a number of small-scale trials in patients and animal models (Table 3). Studies in animals have largely supported the hypothesis that glucocorticoid administration will reduce neointimal proliferation. Systemic dexamethasone administration inhibited neointimal lesion formation in rats (Villa *et al.*, 1994; Guzman *et al.*, 1996),

Table 3 The effect of glucocorticoid administration on vascular remodeling

Study sample	*Study design & intervention*	*Outcome*	*Reference*
Clinical Studies			
PCI	Patients with ACS; D-DES implantation	Reduced clinical events (6 months); No antirestenotic effect	(Ribichini *et al.*, 2007b)
PCI + stent	Oral prednisone (45 days) in patients with high CRP	Reduced clinical events and angiographic restenosis rate	(Versaci *et al.*, 2002)
	Oral prednisone, low dose vs high dose	Low dose less effective	(Ferrero *et al.*, 2007b)
	Intra-wall delivery of methylprednisolone before elective stent implantation	No reduction in the incidence of restenosis	(Reimers *et al.*, 1998)
Stent	Dex	Increased Aneurysm	(Rab *et al.*,1991)
		No effect	(Stone *et al.*, 1989)
		No effect	(Pepine *et al.*, 1990)
	Oral Methylprednisolone (1 g)	No effect	(Lee *et al.*, 1999)
	High dose Dex	No effect	(Hoffmann *et al.*, 2004b)
	Hydrocortisone (200 mg)	Reduced coronary restenosis	(Kakio *et al.*, 2004)
	Dexamethasone (low dose)	Low restenosis rate	(Liu *et al.*, 2003)
Animal Studies			
Dog	D-DES-coated stent	Reduced neointimal proliferation	(Strecker *et al.*, 1998)
Pig	Stent (Dex)	No effect	(Lincoff *et al.*, 1997)
Rat	Local Dex administration	Reduced neointimal proliferation	(Villa *et al.*, 1994b)
		Reduced neointimal proliferation	(Guzman *et al.*, 1996)
		Reduced neointimal proliferation	(Petrik *et al.*, 1998)
		Increased neointimal proliferation via increased ACE.	(Fishel *et al.*, 1995)
Rabbit	Dex (1 $mg \cdot kg^{-1} \cdot day^{-1}$) oral or sc (2 weeks) after silicone collar induced injury to the carotid artery	Reduced neointimal proliferation	(Van Put *et al.*, 1995)
	Systemic (2.1 $mg \cdot kg^{-1} \cdot day^{-1}$) or local prednisone	Reduced neointimal proliferation	(Ribichini *et al.*, 2007a)
Rabbit (high fat)	Dex (1 $mg \cdot kg^{-1} \cdot day^{-1}$) (one week); bilateral iliac artery endothelial denudation, followed by angioplasty	No effect on intimal hyperplasia or fibrosis	(Karim *et al.*, 1997)

ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; Dex, dexamethasone; D-DES, dexamethasone-drug eluting stent; PCI, Percutaneous coronary intervention.

rabbits (Van Put *et al.*, 1995; Poon *et al.*, 2001) and dogs (Strecker *et al.*, 1998) with inhibition of macrophage accumulation proposed as a possible mechanism of action (Poon *et al.*, 2001). Similar results were obtained with either oral or local prednisone in rabbit iliac artery (Ribichini *et al.*, 2007a). This approach may also have potential in the prevention of chronic graft disease as short-term (7 days) oral dexamethasone (0.15 $mg^{-1} \cdot kg^{-1} \cdot day^{-1}$) reduced vein graft thickening in ApoE3leiden mice (Schepers *et al.*, 2006). Not all studies in animals have yielded positive results, however, as dexamethasone treatment did not reduce neointimal hyperplasia after angioplasty in the rabbit (Karim *et al.*, 1997) or in the pig (Lincoff *et al.*, 1997). Initial clinical trials were also disappointing: methylprednisolone did not inhibit restenosis after coronary angioplasty (Pepine *et al.*, 1990) or stenting (Reimers *et al.*, 1998) while dexamethasone-drug eluting stents (D-DES) have not reduced the incidence of restenosis (Hoffmann *et al.*, 2004a; Ribichini *et al.*, 2007b). The reasons for the differences between animals and humans remain unclear but there are several possible explanations, including: animal models providing a poor approximation of disease in humans; clinical trials using small numbers of patients, often with refractory or complex disease; differences in timing of drug administration in animal and clinical studies, and; detrimental systemic effects of glucocorticoids masking beneficial effects in the arterial wall. More recently, interest in the potential of glucocorticoids as anti-restenotics has been re-awakened (Liu *et al.*, 2004; Radke *et al.*, 2004; Ferrero *et al.*, 2007a) with several trials suggesting a beneficial effect of glucocorticoids: oral prednisone produced a dose-dependent reduction in clinical events and angiographic restenosis rate after stenting (the IMPRESS trial) (Versaci *et al.*, 2002; Ferrero *et al.*, 2007b); low-dose dexamethasone was associated with low restenosis rate (the STRIDE trial) (Liu *et al.*, 2003), D-DES produced a low rate of clinical events at 6 months (despite no inhibition of restenosis; the DESIRE trial) (Ribichini *et al.*, 2007b). It should be noted, however, that the EMPEROR trial was discontinued before patient recruitment because of poor results from a pilot study (Hoffmann *et al.*, 2004b). An intriguing addendum to this search for an anti-restenotic capability of glucocorticoids has been the recent announcement of a study designed to test the effect of glucocorticoid administration by encapsulation in erythrocytes (Versaci and Del Giudice; http://clinicaltrials.gov).

Pharmacological inhibition of 11-HSDs in the treatment of cardiovascular disease

Plant-derived and endogenous 11-HSD inhibitors

Inhibition of 11-HSD activity in experimental and clinical studies depended, until relatively recently, upon the use of several naturally occurring compounds (Figure 1B). Principal among these were compounds derived from glycyrrhizic acid, the principal active component of the liquorice plant, *Glycyr-*

rhiza glabra. Indeed, the therapeutic activity of liquorice was well known to the Ancient Greeks and Romans, is exploited in traditional Chinese medicine and, until the introduction of H_2 antagonists in the late 1970s, provided the most effective treatment for peptic ulcers (Davis and Morris, 1991). In addition, excessive liquorice ingestion causes SAME as a result of 11-HSD type 2 inhibition (Conn *et al*., 1968). Glycyrrhetinic acid (Adamson and Tillman, 1955), the hydrolytic product of glycyrrhizic acid, and its hemi-succinate derivative, carbenoxolone (Csonka and Murray, 1971), have anti-inflammatory properties in the skin and have also been used extensively for pharmacological inhibition of 11-HSD activity. The usefulness of these compounds is limited, however, as they inhibit both isozymes of 11-HSD [IC_{50}s: Dehydrogenase activity: glycyrretinic acid; ~2.5×10^{-8} mol·L^{-1}; carbenoxolone ~1.5×10^{-7} mol·L^{-1} (Schleimer, 1991)]; Oxo-reductase; glycyrretinic acid; ~8×10^{-8} mol·L^{-1}; carbenoxolone ~1×10^{-7} mol·L^{-1} (Li *et al*., 1997) although it has been suggested that carbenoxolone is more active against the dehydrogenase activity (Ki 2×10^{-8} mol·L^{-1} compared with 4.1×10^{-7} mol·L^{-1} for the reductase) of 11-HSD (Brem *et al*., 1997; Morris *et al*., 2003). In addition, unwanted effects of carbenoxolone may be mediated by its ability to inhibit 3α-hydroxysteroid dehydrogenase (Akao *et al*., 1992) and to block myoendothelial gap junctions (Goldberg *et al*., 1996; Edwards *et al*., 1999).

In addition to these plant-derived compounds, several endogenous inhibitors of 11-HSD have also been identified. These include the cholesterol derivatives 11β-OH-progesterone and its metabolite 11-keto-progesterone, both of which inhibit 11-HSD; it has been suggested that 11β-OH-progesterone selectively inhibits 11-HSD dehydrogenase activity while 11-keto-progesterone is selective for 11-HSD reductase activity (Brem *et al*., 1997). Both compounds are relatively weak inhibitors ($K_i = 5 \times 10^{-7}$ mol·L^{-1} and 6.8×10^{-7} mol·L^{-1} for 11β-OH-progesterone and 11-keto-progesterone respectively), however, and the claim of selectivity for the latter is contentious. Endogenous bile acids, such as lithocholic acid and chenodeoxycholic acid, are also non-selective inhibitors of 11-HSD (Perschel *et al*., 1991; Latif *et al*., 1994) with the latter proposed to be selective for 11-HSD1 (Morris and Souness, 1996). More recently it has been demonstrated that 11-HSDs can metabolize 7-oxysterols in man and rodents (Hult *et al*., 2004a,b; Schweizer *et al*., 2004b) revealing the possibility that 7-oxysterols may inhibit 11-HSD-mediated metabolism of glucocorticoids by competing for the active site of the enzyme (this work also suggests that 11-HSDs could directly mediate the generation of atherogenic cholesterol metabolites). In general, however, inhibition of 11-HSD by compounds obtained from liquorice (Glycyrrhetinic acid, Glycyrrhizic acid, carbenoxolone), or generated endogenously (e.g. 11β-hydroxyprogesterone; chenodeoxycholic acid), tends to be non-selective or weakly selective.

The limited availability of isozyme-selective 11-HSD inhibitors has prompted the use of alternative approaches to differentiate their physiological roles. Transgenic deletion (Kotelevtsev *et al*., 1997; 1999) and over-expression (Masuzaki *et al*., 2001; 2003; Paterson *et al*., 2004) of 11-HSD isozymes has been invaluable in this respect. In addition, selective 11-HSD inhibition has been achieved using specific anti-sense oligonucleotide probes to 11-HSD1 and 11-HSD2 (Souness *et al*., 1995). The influence of tissue-specific regulation of 11-HSD1 on cardiovascular risk factors [with over-expression of 11-HSD1 in the adipose tissue (Masuzaki *et al*., 2001; 2003) or liver (Paterson *et al*., 2004) producing central obesity, hypertension and dyslipidaemia] and the presence of both isozymes in the heart and blood vessel wall has suggested that they may prove a useful therapeutic target in cardiovascular disease.

Selective 11-HSD inhibitors

The identification of 11-HSD1 as a potential target for the treatment of diabetes mellitus and metabolic syndrome has prompted considerable recent activity in the pharmaceutical industry; leading to the discovery and development of a multitude of novel non-steroidal 11-HSD1-selective inhibitors (>90 patents filed by ~29 different companies and other organizations since 2002). These embrace a wide variety of compounds, based predominantly around: triazoles, aryl sulphonamide thiazoles, sulfonamides and adamantyl carboxamides (Webster and Pallin, 2007; Hughes *et al*., 2008). Development of these new compounds has not been trivial, with the challenge being to find a small molecule that is both potent and selective enough to exploit the extremely hydrophobic pocket in the active site of 11-HSD1 (Hosfield *et al*., 2005; Zhang *et al*., 2005b; Kim *et al*., 2006a). This requires the presence of lipophilic groups which, in most inhibitors, contributes to associated problems with stability and solubility. Both issues, however, have been successfully improved by appropriate chemical modification, producing compounds with good pharmacodynamic and pharmacokinetic profiles in target tissues.

Selective 11-HSD1 inhibitors potentially have a variety of clinical applications [reviewed in Wamil and Seckl (2007)], for example, in the treatment of wound healing and age-related cognitive impairment. Their application in the cardiovascular arena could include treatment of the metabolic syndrome, obesity, type 2 diabetes and prevention and treatment of atherosclerosis. It is recognized that pharmacological effects of these compounds on the metabolic syndrome require 11-HSD1 inhibition in the liver and adipose tissue (Webster and Pallin, 2007). Several companies have now produced orally available compounds that achieve inhibition in these tissues in rodents (rats, mice); with tissue inhibition in human adipose also recently demonstrated in phase IIa clinical trials in obese patients [reviewed in Webster and Pallin (2007)].

The therapeutic potential of 11-HSD1 inhibitors in metabolic syndrome (specifically, obesity, type 2 diabetes mellitus and dyslipidaemia) is very promising. For example, based on animal studies showing its ability to restore the glucose lowering action of insulin without influencing HPA axis function, INCB13739 (Incyte corp, Wilmington, Del) has been shown, in phase IIa clinical trials, to rapidly correct glucose levels, improve insulin resistance, fasting cholesterol and low-density lipoprotein levels in patients with type 2 diabetes (Press release Incyte web site; http://incyte.com/index.html). Additionally, phase I clinical trials of selective 11-HSD1 inhibitors have also been disclosed by Amgen and Biovitrum (AMG221) with a pre-clinical trial programme at Pfizer (Biocentury 2007, 15 (4), A1–A25).

11-HSD1 inhibition in cardiovascular disease

11-HSD1 knockout mice have an atheroprotective phenotype, including lower cholesterol and triglyceride levels and improved glucose tolerance (Morton *et al.*, 2001) while non-selective 11-HSD1 inhibition with carbenoxolone (4 weeks) significantly reduced atherosclerosis in mice (Nuotio-Antar *et al.*, 2007). In addition, it is possible that some anti-atherosclerotic interventions owe part of their effectiveness to regulation of 11-HSDs as PPAR-α agonists, such as fibrates (which are important agents for treating dyslipidaemia) reduce 11-HSD1 expression and activity in murine liver (Hermanowski-Vosatka *et al.*, 2000). One concern is raised, however, by the ability of 11-HSD1 to metabolise 7-oxysterols, as this may be pro-atherogenic (Schroepfer, 2000). 7-Ketocholesterol which is present in very small quantities in the plasma is highly concentrated in human atherosclerotic lesions (Brown *et al.*, 2000) and is linked with an increased risk of developing atherosclerotic plaques at an early age as demonstrated in patients with cerebrotendinous xanthomatosis (Fujiyama *et al.*, 1991). 11-HSD1 inhibition *in vivo* results in increased 7-ketocholesterol levels in the liver and plasma in rats (Schweizer *et al.*, 2004a,b).

Initial results from *in vivo* studies in mouse and rat models have produced promising evidence that selective 11-HSD1 inhibitors provide an effective treatment for systemic cardiovascular risk factors, including: obesity, type 2 diabetes and dyslipidaemia. It has been established that exposure to 11-dehydrocorticosterone can induce an 11-HSD1-dependent, GR-dependent increase in pancreatic 11-HSD1 activity, leading to reduced glucose-mediated insulin secretion from pancreatic islets (Wang *et al.*, 2004; Ortsater *et al.*, 2005). In addition, 11-HSD1 inhibition (with BVT: 2733) improved insulin sensitivity and dyslipidaemia [200 $mg \cdot kg^{-1}$ twice daily; Alberts *et al.*, 2003] and decreased blood glucose [7 day administration by minipump; Alberts *et al.*, 2002] in hyperglycaemic mice. Perhaps the most striking example of the benefit of selective 11-HSD1 inhibition in mouse models of disease is provided by a study with an inhibitor (Compound 544), produced by Merck Laboratories, that produces short-term selective inactivation of 11-HSD1 after oral administration (Hermanowski-Vosatka *et al.*, 2005). This investigation confirmed that 11-HSD1 inhibition was beneficial in mice with diet-induced obesity and streptozotocin/high-fat diet-induced diabetes (reducing body weight, fasting glucose and serum lipids) after twice daily administration (20 or 30 $mg \cdot kg^{-1}$) for only 11 days. In addition, extended (8 week) administration of this compound (~10 $mg \cdot kg^{-1} \cdot day^{-1}$) to atherosclerosis prone (Apolipoprotein E knockout) mice on a high-fat diet lowered serum cholesterol, triglycerides and free fatty acids and produced a dramatic (~85%) reduction in atherosclerotic lesion development. Improvements in cardiovascular risk factors are not restricted to this compound or to mouse models as a low dose (3 $mg \cdot kg^{-1} \cdot day^{-1}$) of a 4-heteroarylbicyclo [222] octyl triazole compound improved fasting triglyceride levels and prevented lipid accumulation in tissues of rats with diet-induced obesity (Berthiaume *et al.*, 2007a,b). These pre-clinical studies are now being augmented by the first clinical trials, for example the phase IIa trials with compound INCB13739 in patients with type 2 diabetes (see above: Incyte Press Release; http://incyte.com/index.html).

The mechanisms through which selective 11-HSD1 inhibitors reduce atherosclerosis have yet to be demonstrated unequivocally. It was notable that the dramatic reduction in lesion formation produced by Compound 544 in atherosclerotic mice was greater than predicted by the more modest improvements in systemic metabolic risk factors (Hermanowski-Vosatka *et al.*, 2005). Similarly carbenoxolone-mediated inhibition of atherogenesis was independent of blood pressure (Nuotio-Antar *et al.*, 2007). It was proposed, therefore, that 11-HSD1 inhibition may have a direct protective effect on the vascular wall (Hermanowski-Vosatka *et al.*, 2005). If this is the case, the precise mechanisms have not been established although data were provided to suggest that 11-HSD1 inhibition was reducing concentrations of MCP-1 in the circulation and aortic wall [MCP-1 is not normally found in the arterial media or intima but has been found in human and rodent atherosclerotic plaques (Ylaherttuala *et al.*, 1991)]. This is not consistent, however, with the reported GR-dependent inhibition of MCP-1 from arterial SMC by glucocorticoids (Dhawan *et al.*, 2007). Furthermore, the role of 11-HSD1 in regulating the inflammatory response to injury or proliferation and migration of VSMCs *in vivo* has not been investigated in models of neointimal proliferation. We have shown recently (Dover *et al.*, 2007), however, that intraluminal injury followed by neointimal remodelling does not appear to produce the up-regulation of 11-HSD1 activity [or increased sensitivity to pro-inflammatory cytokines (Figure 3E)] reported in cultured VSMC (Cai *et al.*, 2001). Finally, it should be noted that our recent demonstration that endogenous 11-HSD1 activity suppresses angiogenesis following myocardial infarction (Small *et al.*, 2005) suggests that 11-HSD1 inhibition is likely to promote neovascularization following infarct with consequent improvements in cardiac function. Whether this will actually prove to be the case has yet to be determined.

Conclusions

While it is evident that glucocorticoids can influence the development of cardiovascular disease the processes involved are complex and incompletely understood. The ability of glucocorticoids to stimulate both GR and MR, to mediate opposing actions depending on steroid concentration, and to regulate systemic cardiovascular risk factors as well as functional and structural properties of cardiac, vascular and inflammatory cells makes it difficult to determine which mechanisms contribute to regulation of cardiovascular disease pathogenesis. Thus, it is still not clear why, despite the association between glucocorticoid excess and cardiovascular disease, glucocorticoid administration inhibits atherogenesis and restenosis in animal models. The situation is further complicated by the role of tissue-specific regulation of glucocorticoid activity by the 11-HSDs which introduces the possibility of local glucocorticoid deficiency/excess. The importance of 11-HSDs does, however, provide a potentially important novel therapeutic target. Traditional pharmacological approaches to regulation of glucocorticoid activity are limited by the varied systemic actions of these steroids and, thus, the multiplicity of complications associated with

manipulation of this system. Targetting 11-HSD isozymes raises the possibility of tissue-specifc manipulation of 11-HSD activity without altering regulation of the HPA axis.

The potential implications of 11-HSD1 inhibition in treatment of cardiovascular disease have been difficult to predict given the complex relationship between glucocorticoids and this condition. Evidence from transgenically modified mice and a small number of studies using relevant inhibitors, have suggested that 11-HSD1 inhibition should reduce cardiovascular disease by reducing systemic cardiovascular risk factors. Theoretically, these inhibitors also have the potential to alter glucocorticoid activity in the heart, inflammatory cells and vascular wall: whether these actions are all desirable in prevention of atherosclerosis, and whether they contribute to the anti-atherosclerotic action of 11-HSD1 inhibitors has not been determined. Perhaps most importantly, however, much of the evidence that 11-HSD activity regulates cardiovascular disease comes from animal models. There is, as yet, only a superficial understanding of the role of 11-HSDs in regulating atherosclerosis and remodelling following infarction in humans. Given the current enthusiasm for generation and clinical testing of selective 11-HSD1 inhibitors for the treatment of metabolic conditions associated with cardiovascular disease, it is clearly imperative to develop an improved understanding of the action of glucocorticoids, and their endogenous metabolism by 11-HSD isozymes, on cardiovascular pathophysiology. The influence of endogenous glucocorticoid activity, and its regulation within the heart and vascular wall, on atherosclerosis, restenosis and cardiac infarction needs to be demonstrated. Understanding this relationship, particularly in man, will be key to confirming the mechanisms underlying the anti-atherosclerotic actions of selective 11-HSD1 inhibitors and predicting possible side effects.

Conflicts of interest

P.W.F.H. and B.R.W. are inventors on relevant patents owned by the University of Edinburgh. B.R.W. has received speaker's honoraria from Abbott, Bristol Myers Squibb, Merck and Novartis and consulted for Amgen, AstraZeneca, Biovitrum, Dianippon, Incyte, Ipsen, Johnson & Johnson, Merck, Roche, Syrrx, Vitae, Wyeth, and Zydus. J.I. has no conflicts of interest.

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