Glucocorticoids and Cardiovascular Disease

Brian R Walker
Endocrinology Unit, Queen’s Medical Research Institute, Centre for Cardiovascular Science, University of Edinburgh, 47 Little France Crescent, Edinburgh EH16 4TJ, Scotland, UK

(Correspondence should be addressed to B R Walker; Email: b.walker@ed.ac.uk)

This article is based on the presentation for the European Journal of Endocrinology Prize Lecture 2004 at the European Society of Endocrinology Meeting at Budapest, Hungary

Abstract
Chronic excessive activation of glucocorticoid receptors induces obesity, insulin resistance, glucose intolerance, dyslipidaemia and hypertension. Subtle abnormalities of the hypothalamic–pituitary–adrenal axis and/or of tissue sensitivity to glucocorticoids are also associated with these cardiovascular risk factors in patients with the metabolic syndrome. Furthermore, glucocorticoids have direct effects on the heart and blood vessels, mediated by both glucocorticoid and mineralocorticoid receptors and modified by local metabolism of glucocorticoids by the 11β-hydroxysteroid dehydrogenase enzymes. These effects influence vascular function, atherogenesis and vascular remodelling following intravascular injury or ischaemia. This article reviews the systemic and cardiovascular effects of glucocorticoids, and the evidence that glucocorticoids not only promote the incidence and progression of atherogenesis but also modify the recovery from occlusive vascular events and intravascular injury. The conclusion is that manipulation of glucocorticoid action within metabolic and cardiovascular tissues may provide novel therapeutic avenues to combat cardiovascular disease.

European Journal of Endocrinology 157 545–559

Introduction
Atherosclerosis and its occlusive vascular consequences remain the most common cause of death in many parts of the world. Several risk factors for the development of atheroma are amenable to treatment, including hypercholesterolaemia, hypertension, hyperglycaemia and cigarette smoking. Secular trends show that cardiovascular disease is declining in prevalence in the developed world, and that the outcome from events such as myocardial infarction is improving, in part due to modern cardiological interventions (1). However, there is concern that the pandemic of obesity and associated metabolic syndrome threatens to reverse these secular trends. In order to make further improvements in the prevalence and outcome of occlusive vascular disease and avoid the threat posed by obesity, we will need to understand more about the complex mechanisms that promote atheromatous plaque formation and instability and determine recovery following occlusive vascular events. This review is focused on the role of glucocorticoids in atherogenesis, and highlights emerging data which suggest that manipulation of glucocorticoid action has important potential in improving the outcome of occlusive vascular disease.
lower levels. In some sites (such as distal nephron, colon, salivary and sweat glands and vascular endothelium), MRs bind aldosterone exclusively because cortisol is excluded by local ‘pre-receptor’ inactivation by 11β-HSD2 (which converts cortisol to the inert 11-keto metabolite cortisone; Fig. 1B) (3). In other sites (classically in hippocampus and also probably in myocardium, vascular smooth muscle and adipose tissue), in the absence of 11β-HSD2, intracellular cortisol concentrations are reduced, excluding cortisol from both MR and GR and allowing access of aldosterone to MR. Examples are in the distal nephron, colon and sweat glands and in vascular endothelial cells. (C) In the presence of 11β-HSD1, intracellular cortisol concentrations are increased. Occupancy of MR by cortisol may not increase, since capacity is limited, but occupancy of GR by cortisol is increased. Examples include vascular smooth muscle cells. 11β-HSD1 is also commonly expressed in cells which express GR but not MR, including hepatocytes, adipocytes, some areas of CNS and macrophages. (D) Tissue-specific differences in expression of 11β-HSDs may contribute to tissue-specific differences in glucocorticoid sensitivity in subjects with subtle alterations in GR (Table 1). In cells expressing 11β-HSD1 (C) or 11β-HSD2 (B), actions of GR may not be affected by a subtle shift in the dose–response curve because intracellular cortisol concentrations are at the extreme ends of the dose–response curve where the response induced by mutant GR is not markedly different from wild type.

These classical intracellular MRs and GRs act as transcription factors on ~30% of genes, with the pattern of response in individual cell types dictated by the enormous complexity of interactions with heterodimers, co-activators and co-repressors, and epigenetic factors including chromatin organisation. To add to this complexity, there may be a role for non-genomic membrane receptor-mediated responses to glucocorticoids, but this remains of uncertain physiological relevance (6). Note that synthetic steroids vary in their susceptibility to metabolism by 11β-HSDs and in their binding affinities for GR and MR (7): 9α-fluorocortisol (‘fludrocortisone’) resists metabolism by 11β-HSD2 but retains activity at both GR and MR, prednisolone is susceptible to metabolism by 11β-HSDs but is relatively selective for GR over MR, and dexamethasone is relatively resistant to 11β-HSDs (8) and a potent selective GR agonist.

The metabolic effects of glucocorticoids in the liver, adipose tissue, pancreas and brain have been reviewed elsewhere (9–11): broadly, glucocorticoids oppose the effects of insulin and increase turnover between stored energy (in glycogen, triglycerides and protein) and freely available fuel for mitochondrial oxidation (glucose and free fatty acids). Glucocorticoids also raise blood pressure, only in part mediated by renal sodium retention and plasma volume expansion (12, 13). In addition, both GR and MR are expressed in cardiovascular tissues including the heart and arterial walls, where glucocorticoids act directly to maintain vascular tone and modify vascular inflammatory, proliferative and remodelling responses to injury (see below, reviewed in (14–16)).
Glucocorticoids and risk factors for cardiovascular disease

During chronic activation of the HPA axis, the effects of glucocorticoids may become maladaptive (17, 18). The metabolic and cardiovascular consequences are apparent in Cushing’s syndrome, which is characterised by central obesity, insulin resistance, hyperglycaemia, dyslipidaemia and hypertension. Given the similarities between Cushing’s syndrome and the metabolic syndrome, subtle abnormalities of cortisol secretion and action have been sought in subjects with this constellation of risk factors for cardiovascular disease (19).

The HPA axis

Activation of the HPA axis, with increased cortisol secretion rate and elevated morning plasma cortisol levels, has been associated with higher plasma glucose, triglycerides and blood pressure in several population-based cohort studies (20). Relationships of plasma cortisol with obesity, however, are more complex, since obesity is associated with increased metabolic clearance rate of cortisol, which tends to lower plasma cortisol levels despite enhanced cortisol production rate (20). As a result, elevated plasma cortisol and obesity have independent and additive effects in predicting cardiovascular risk factors (21, 22).

Since it was popularised by Per Bjorntorp (23), the concept has spread that central obesity and metabolic syndrome are consequences of psychosocial stress, mediated by neuroendocrine stress responses including activation of the HPA axis. However, empirical evidence is inconsistent concerning the role of psychosocial stress – and, in particular, its role as the basis for HPA axis activation – in metabolic syndrome (24, 25). An alternative hypothesis is that activation of the HPA axis is a phenomenon ‘programmed’ by adverse events during early life which retard fetal growth. This is supported by associations between low birth weight and elevated plasma cortisol in adulthood, both in the basal state (26–28) and in response to stress (29–31). The molecular basis for this HPA axis activation remains uncertain, although it may involve epigenetic modification affecting transcription of GR (32, 33).

Tissue sensitivity to cortisol

In addition to control of cortisol action by the HPA axis, tissue sensitivity to cortisol may vary both between individuals and between tissues. Arguably, our understanding of the factors controlling tissue sensitivity to glucocorticoids (see above and Fig. 1) is simplistic, but we are at least beginning to understand the influence of variation in corticosteroid receptors and in pre-receptor steroid metabolism.

Simple bioassays, e.g. measuring the intensity of dermal vasoconstriction after overnight steroid application, suggest that tissue sensitivity to glucocorticoids is increased amongst subjects with cardiovascular risk factors (34–37). In part, this may be determined by variations in GR function (36). In metabolic syndrome, GR mRNA has been reported to be increased in skeletal muscle (38, 39) but not in adipose tissue (40). As detailed in Fig. 2 and Table 1, polymorphisms in the GR gene, which influence in vitro receptor function, have been associated with cardiovascular risk factors including obesity (41). One might imagine that changes in GR function would not be cell-type specific, so that any change in sensitivity to cortisol in peripheral tissues would be compensated for by altered negative feedback control of the HPA axis and hence adjustment of circulating cortisol levels. Indeed, in very rare families with mutations in the GR gene causing autosomal dominant cortisol resistance, the resistance to cortisol does appear to be sufficiently uniform that the phenotype can be explained by increased ACTH secretion and hence excessive adrenal production of mineralocorticoids (11-deoxycorticosterone) and androgens (42, 43). However, the GR polymorphisms shown in Fig. 2 and Table 1 probably influence interactions between GR and other transcription factors, and may not induce uniform changes in receptor signalling; indeed, the effects may be not only tissue specific but potentially gene specific. This is exemplified in the case of the Bcl1 polymorphism, which increases sensitivity of cortisol suppression by dexamethasone and of skin vasoconstriction by beclo-methasone but paradoxically is associated with elevated plasma cortisol concentration (Table 2). Moreover, in vitro dose–response curves suggest that these polymorphisms are associated with subtle changes in sensitivity but not in maximum response to GR activation (44). The model in Fig. 1D illustrates that
Table 1 Associations of genetic variation in the glucocorticoid receptor gene (see Fig. 2)\textsuperscript{a} with cardiovascular risk and disease.

<table>
<thead>
<tr>
<th>Allele frequency in population</th>
<th>ER22/23EK</th>
<th>N363S</th>
<th>Bcl I RFLP G allele</th>
<th>A/G 3669</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro glucocorticoid sensitivity</td>
<td>~5%</td>
<td>~6%</td>
<td>Enhanced sensitivity to Dex in PMN cell proliferation assay (161)</td>
<td>No effect on GR binding or number of PMN cells (36, 161)</td>
</tr>
<tr>
<td>Proposed molecular mechanism</td>
<td>Increased GR-A:G-R-B transcript ratio (165)</td>
<td>?</td>
<td>Enhanced Dex suppression (161)</td>
<td>Impaired transrepression but normal transactivation in PMN (44)</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Higher lean body mass (167); insulin sensitivity (162); protective lipid profile (162); lower CRP (168); reduced mortality (168); cognitive protection (169)</td>
<td>Obesity in some (161, 170–173) but not all (174, 175) cohorts; dyslipidaemia (116); coronary artery disease (116)</td>
<td>Inconsistent with obesity (36, 163, 164, 176–180); hyperinsulinaemia in obese (181); familial hypertension (182)</td>
<td>Stabilisation of dominant negative GRb (166)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}A TthIII RFLP was also reported upstream of the promoter in association with elevated cortisol levels but no other phenotype has been found in other populations (174).

\textsuperscript{b}Lesions, notably in macrophages (66). We have present in inflammatory cells, which invade vascular and myocardial tissue (reviewed in (14–19)). Lower levels of 11b-HSD1 and 11b-HSD2 in macrophages (67, 68), although this distribution may vary somewhat between species and distribution in inflammatory cells (69, 70), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 68), although this is expressed in differentiated macrophages (67, 71), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). 

\textsuperscript{c}Lesions, notably in macrophages (66). We have present in inflammatory cells, which invade vascular and myocardial tissue (reviewed in (14–19)). Lower levels of 11b-HSD1 and 11b-HSD2 in macrophages (67, 68), although this distribution may vary somewhat between species and distribution in inflammatory cells (69, 70), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). 

\textsuperscript{d}Lesions, notably in macrophages (66). We have present in inflammatory cells, which invade vascular and myocardial tissue (reviewed in (14–19)). Lower levels of 11b-HSD1 and 11b-HSD2 in macrophages (67, 68), although this distribution may vary somewhat between species and distribution in inflammatory cells (69, 70), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). 

\textsuperscript{e}Lesions, notably in macrophages (66). We have present in inflammatory cells, which invade vascular and myocardial tissue (reviewed in (14–19)). Lower levels of 11b-HSD1 and 11b-HSD2 in macrophages (67, 68), although this distribution may vary somewhat between species and distribution in inflammatory cells (69, 70), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). 

\textsuperscript{f}Lesions, notably in macrophages (66). We have present in inflammatory cells, which invade vascular and myocardial tissue (reviewed in (14–19)). Lower levels of 11b-HSD1 and 11b-HSD2 in macrophages (67, 68), although this distribution may vary somewhat between species and distribution in inflammatory cells (69, 70), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). 

\textsuperscript{g}Lesions, notably in macrophages (66). We have present in inflammatory cells, which invade vascular and myocardial tissue (reviewed in (14–19)). Lower levels of 11b-HSD1 and 11b-HSD2 in macrophages (67, 68), although this distribution may vary somewhat between species and distribution in inflammatory cells (69, 70), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). 

\textsuperscript{h}Lesions, notably in macrophages (66). We have present in inflammatory cells, which invade vascular and myocardial tissue (reviewed in (14–19)). Lower levels of 11b-HSD1 and 11b-HSD2 in macrophages (67, 68), although this distribution may vary somewhat between species and distribution in inflammatory cells (69, 70), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). 

\textsuperscript{i}Lesions, notably in macrophages (66). We have present in inflammatory cells, which invade vascular and myocardial tissue (reviewed in (14–19)). Lower levels of 11b-HSD1 and 11b-HSD2 in macrophages (67, 68), although this distribution may vary somewhat between species and distribution in inflammatory cells (69, 70), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). 

\textsuperscript{j}Lesions, notably in macrophages (66). We have present in inflammatory cells, which invade vascular and myocardial tissue (reviewed in (14–19)). Lower levels of 11b-HSD1 and 11b-HSD2 in macrophages (67, 68), although this distribution may vary somewhat between species and distribution in inflammatory cells (69, 70), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16). Low levels of 11b-HSD1 and 11b-HSD2 in the endothelium (67, 68) of vascular smooth muscle cells (67, 71), reviewed in (16).
vascular endothelial cells may follow Fig. 1B, vascular smooth muscle cells may follow Fig. 1C, and macrophages may follow Fig. 1C (but with only GR and not MR present). There have also been sporadic reports that vascular tissue and myocardium express the enzymes necessary for de novo steroidogenesis from cholesterol (72, 78, 79), although the magnitude, if any, of this contribution appears to be very small.

The effects of glucocorticoids on cardiovascular tissues are summarised in Table 2, which shows diverse effects on vascular development, remodelling, tone and inflammation. There are substantial weaknesses in this field, however, since very few experiments have dissected systemic (e.g. actions in liver or kidney) from local (intravascular) effects of either glucocorticoids or mineralocorticoids, it has been difficult to recapitulate in vivo findings in experiments in isolated vessels in vitro, and the potential for occupancy of MR as well as GR by cortisol has not always been taken into account in interpretation of results.

The influence of 11β-HSDs on vascular function has been addressed using non-selective enzyme inhibitors (80–83), antisense knockdown (84) and in global “knockout” mice (68, 85) but not yet by cell-specific manipulations of 11β-HSDs. While loss of 11β-HSD2 dehydrogenase inactivation of glucocorticoid in the endothelium was associated with enhanced vasoconstrictor responses, loss of 11β-HSD1 reductase regeneration of glucocorticoid in vascular smooth muscle did not influence vascular tone. More recent studies suggest that 11β-HSD1 influences remodelling responses in the vasculature (see below (63, 86)). In vascular cells and macrophages in vitro, pro-inflammatory cytokines up-regulate 11β-HSD1 expression (76, 77, 87), raising the intriguing possibility that local amplification of cortisol concentrations provides a counter-regulatory response which modifies remodelling during vascular injury or inflammation. However, in in vivo studies we were unable to confirm this phenomenon (88).

Against this background, the responses to glucocorticoids within the blood vessel wall will reflect the balance between access of ligands to MR and GR, between systemic versus local effects, and between other complex determinants of receptor interaction with gene transcription and ‘non-genomic’ signalling alluded to above. The role of glucocorticoids in the incidence and progression of cardiovascular disease is therefore unpredictable.

### Glucocorticoids and incidence of occlusive vascular disease

#### Exogenous anti-inflammatory glucocorticoids

Despite their effects to induce cardiovascular risk factors, studies in animals have suggested that medium-term GR-agonist therapy is atheroprotective in mice (89) and rabbits (90, 91), as judged by markers such as aortic cholesterol content or cellular proliferation indices. Conversely, aldosterone reportedly increases, and MR antagonists decrease, atherogenesis in mice (92, 93). Further, glucocorticoid excess may promote calcification within arteriosclerotic lesions (94). In humans, a major concern has been that anti-inflammatory glucocorticoid therapy induces atherogenesis in patients with inflammatory diseases (95, 96). Indeed, there appears to be a dose–response relationship between cumulative exposure to glucocorticoids and the prevalence of carotid artery atheroma visualised by ultrasound amongst patients with rheumatoid arthritis (97). It has been difficult, however, to confidently dissect effects of glucocorticoids from those of the underlying inflammatory disease, which may itself be pro-atherogenic.

Glucocorticoid therapy for inflammatory disease was adopted before the era of randomised controlled trials

---

Table 2 Cardiovascular effects of glucocorticoids.

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Via glucocorticoid receptors</th>
<th>Via mineralocorticoid receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular smooth muscle</td>
<td>⬆ contractility e.g. to noradrenaline (185)</td>
<td>⬆ perivascular inflammation (186)</td>
</tr>
<tr>
<td></td>
<td>⬇ proliferation (138–140)</td>
<td>⬇ vasoconstriction (153)</td>
</tr>
<tr>
<td></td>
<td>⬇ migration (141)</td>
<td></td>
</tr>
<tr>
<td>Endothelial cell</td>
<td>⬇ endothelium-dependent vasodilatation (160)</td>
<td>⬇ vasodilatation (153)</td>
</tr>
<tr>
<td></td>
<td>⬇ angiogenesis (86, 134)</td>
<td></td>
</tr>
<tr>
<td>Myocardium</td>
<td></td>
<td>⬆ fibrosis (133, 187)</td>
</tr>
<tr>
<td>Macrophage</td>
<td>⬇ cytokines (188)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>⬆ apoptosis (189)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>⬇ phagocytosis of apoptotic neutrophils (66)</td>
<td></td>
</tr>
<tr>
<td>Non-cardiovascular organs</td>
<td>Obesity</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyslipidaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin resistance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucose intolerance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prothrombotic</td>
<td></td>
</tr>
</tbody>
</table>

Published data show effects of corticosteroids to: ↑, increase; ↓, decrease; or ±, either increase or decrease.
(RCTs). Although some short-term RCTs have been conducted for example to assess efficacy of low-dose glucocorticoids as disease modifiers in early rheumatoid arthritis (98), it seems certain that RCTs will never be conducted which have sufficient statistical power and duration of exposure to detect effects of glucocorticoids on cardiovascular events. It would be considered unethical to withhold glucocorticoid therapy from patients with inflammatory disease, and unethical to expose patients who do not need anti-inflammatory therapy to the known adverse effects of glucocorticoids (fractures, hyperglycaemia, etc.) (98). In the absence of RCTs, the next best approach is by pharmacoepidemiology. Since glucocorticoids are one of the most commonly prescribed classes of drugs, they lend themselves to this approach. We have conducted two studies to examine the relationship between glucocorticoid therapy and cardiovascular events, making use of the data collected in the universal National Health Service in the UK (99, 100).

The first study was conducted using a case–control design comparing > 50 000 patients with cardiovascular disease and the same number of matched controls in the General Practice Research Database in England (99). In order for data to be collected, participants needed to be in contact with their primary care physician (general practitioner). For this reason, the study was conducted amongst patients who were all receiving glucocorticoid therapy of some kind, and the analysis compared doses of glucocorticoids received in the two groups. The odds ratio for use of oral glucocorticoid therapy (rather than topical or inhaled glucocorticoid therapy) in the group with cardiovascular disease was 1.31 (95% confidence intervals 1.21–1.29).

The second study was conducted using a population-based cohort design in > 150 000 residents of the Tayside region in Scotland (100) for whom data were collected in the Medicines Monitoring Unit for all drugs prescribed (which are identifiable because all pharmacy dispensing is recorded) and for morbidity and mortality from a variety of integrated databases. The rate of incident cardiovascular disease was ~ 17/1000 patient-years in subjects not exposed to glucocorticoids but rose to ~ 24/1000 patient-years in subjects treated with glucocorticoids by any route. Once adjusted for confounders (Fig. 3), the excess cardiovascular risk was entirely attributable to the relatively small group (~ 2% of the population) exposed to supraphysiologic doses of glucocorticoids (> 7.5 mg prednisolone or its equivalent each day), in whom the adjusted relative risk of cardiovascular events was 2.56 (2.18–2.99).

Although the primary end point of these studies was the occurrence of any cardiovascular event, we also examined rates of different events. Notably, glucocorticoids were most strongly associated with occurrence of heart failure and least strongly with cerebrovascular disease events (99, 100). This finding is consistent with the suggestion that glucocorticoids impair recovery from ischaemic events, for example by inhibiting collateral angiogenesis and/or by increasing myocardial fibrosis (see below).

The greatest limitation of the pharmacoepidemiological approach is ‘confounding by indication’, i.e. the possibility that the risk is attributable to the underlying disease being treated rather than to the use of glucocorticoids. In both of our studies (99, 100), effects were consistent across different disease indications. Adjustment for smoking did not substantially attenuate the effect of glucocorticoids. However, in other studies involving cohorts of patients with rheumatoid arthritis, there is some evidence of interactions between effects of glucocorticoids and the underlying inflammatory disease on cardiovascular risk. In a Canadian cohort of > 40 000 subjects, no excess risk of heart failure with glucocorticoid exposure was identified (101). In a smaller US cohort, a dose-dependent risk of cardiovascular disease with glucocorticoid exposure was confirmed, but was only detectable amongst rheumatoid factor-positive patients (102). Studies in other disease groups have probably been too small to be confident of their findings. For example, in one cohort (n = 136) of polymyalgia/giant cell arteritis patients, glucocorticoid therapy predicted increased cardiovascular risk (103), but in another cohort (n = 364) this effect was not seen (104).

Intriguingly, adjustment for the presence of components of the metabolic syndrome (hypertension, diabetes mellitus and dyslipidaemia) did not eliminate

![Figure 3](https://via-free-access.sciencemag.org/doi/10.1124/jb.068905) Cardiovascular disease risk in patients receiving anti-inflammatory glucocorticoid therapy. In a population-based cohort study, the incidence of cardiovascular events was recorded in 68 781 adults > 40 years old receiving therapy with glucocorticoids and 82 202 adults not receiving glucocorticoids during a 4-year follow-up period. Daily glucocorticoid dose was quantified as low (inhaled, nasal and topical steroid only), medium (oral, rectal or parenteral doses < 7.5 mg prednisolone equivalent per day) or high (≥ 7.5 mg prednisolone equivalent per day). The rate ratio is shown after adjustment for age, sex, social deprivation, diabetes mellitus, use of cardiovascular drugs, non-cardiovascular hospitalisation, cancer, renal disease and use of anti-rheumatic and bronchodilator therapy. Reproduced with permission from (100). TIA, transient ischaemic attack.
the effect of glucocorticoids (99, 100, 103), raising the possibility that the influence of glucocorticoids on cardiovascular outcome is not mediated exclusively by known cardiovascular risk factors and might be aggravated by actions in the blood vessel wall.

**Exogenous glucocorticoid replacement therapy**

Although representing a small minority of patients being treated with glucocorticoids, in endocrinology practice we are concerned with patients with hypopituitarism or adrenocortical failure receiving replacement doses of glucocorticoids. The most commonly used steroids for replacement therapy are cortisol (hydrocortisone) or the pre-hormone cortisone (which is ‘activated’ to cortisol by 11β-HSD1 on first pass through the liver). Notably, replacement therapy usually involves non-selective GR/MR agonists (cortisol), by contrast with anti-inflammatory therapy, which usually involves selective GR agonists (prednisolone, etc.). The pharmacokinetics of cortisol, which has high bioavailability and a short half-life (~90 min), makes it impossible to replicate physiological circulating cortisol levels (105), especially since the normal peak of circulating cortisol occurs in advance of waking each morning. In order to achieve sufficiently prolonged effects after each dose, without excessively frequent daily dosing, most patients take doses that induce a supraphysiological level for the first hour or two after dosing. There is evidence from measurement of total cortisol metabolite excretion in urine that these ‘standard’ daily doses are supraphysiological (106), and indeed there is a dose-dependent risk of associated cardiovascular risk factors including obesity and dyslipidaemia (107). By comparison with ‘reference’ values in the population, cardiovascular event rates are reported to be higher in patients with hypopituitarism (108–111) and adrenocortical insufficiency (112). Although there may be several endocrine factors at play, it is plausible to attribute this excess to supraphysiological glucocorticoid therapy.

**Endogenous glucocorticoids**

As described previously, many studies have reported associations between dysfunction of the HPA axis and risk factors for cardiovascular disease in the population. However, data are only now emerging concerning associations between the HPA axis and the occurrence of atheromatous disease. These studies are hampered by the lack of simple measures of HPA axis function which can be applied in large epidemiological studies. Most investigators have relied on fasting plasma cortisol levels, a crude index of HPA axis function. In the Caerphilly Heart Study, Davey-Smith et al. (113) reported a positive association between the plasma cortisol/testosterone ratio and incident vascular disease; cortisol alone was not an independent predictor. In smaller studies, higher plasma cortisol has also been associated with the extent of atheromatous disease quantified by coronary angiography (114), and predicted mortality in patients with heart failure (115). Polymorphisms in the GR gene have recently been associated with cardiovascular event rate in population-based studies in Rotterdam (SWJ Lamberts, personal communication) and Sydney (116) (Table 1).

In spontaneous Cushing’s syndrome, few investigators have accumulated sufficient numbers of patients to generate meaningful data on cardiovascular events. However, intermediate markers, such as carotid intima-media thickness, are abnormal in these patients (117) even after the removal of the tumour responsible for glucocorticoid excess (118).

**Reducing glucocorticoid action and atheroprotection**

Given the association of elevated glucocorticoid action with obesity, cardiovascular risk factors and occlusive vascular disease events, it seems attractive to seek to reduce glucocorticoid action in order to prevent cardiovascular disease. It appears that simultaneous reduction of both GR and MR activation by glucocorticoids has most to offer (Table 2). With respect to reducing GR-dependent signalling, the challenge has been to reduce glucocorticoid action selectively in the blood vessel wall and/or in metabolically important tissues such as liver and adipose tissue, without: i) impairing negative feedback control of the HPA axis, producing compensatory hypercortisolaemia; ii) reducing glucocorticoid action in immune cells, producing a pro-inflammatory state; or iii) preventing an effective cortisol response during stress. Agents that inhibit cortisol biosynthesis or antagonise ligand binding to GR (119, 120) are likely to fail at one of these hurdles. However, inhibition of the cortisol-generating enzyme 11β-HSD1 may be safe and successful (4, 61). Since the enzyme is predominantly expressed in liver and adipose tissue and is also present in vascular smooth muscle, inhibitors may have disproportionately greater effects on metabolism and cardiovascular disease progression than on the HPA axis and the immune system. Moreover, during stress, although 11β-HSD1 inhibitors will reduce the component of intracellular cortisol derived from local regeneration, they should not prevent ‘flooding’ of the cell by cortisol from the circulation during significant hypercortisolaemia. Selective 11β-HSD1 inhibitors have recently been developed and tested in rodents (62–65). In models of obesity and type 2 diabetes, they improve blood glucose, dyslipidaemia, hepatic steatosis, central obesity and insulin sensitivity. Most importantly, in ApoE-deficient mice 11β-HSD1 inhibition produces very striking protection from aortic cholesterol accumulation on Western high-fat diet, which was disproportionate to the improvement in serum lipid profile, suggesting a potent atheroprotective effect potentially mediated in the...
blood vessel wall (63). 11β-HSD inhibitors are now being evaluated in early clinical trials.

**Glucocorticoids and outcomes from occlusive vascular disease**

The role of glucocorticoids in occlusive cardiovascular disease may not be limited to promoting the development and progression of atheroma. Glucocorticoids may also influence the outcomes after plaque rupture, thrombotic occlusion and other vascular injury.

**Recovery from myocardial infarction**

Given their anti-inflammatory effects, glucocorticoids have been proposed to be useful in reducing tissue damage after myocardial infarction (122). However, as noted above, the mechanisms of glucocorticoid action are complex. On one hand, acute induction of endothelial nitric oxide synthase, putatively through ‘non-genomic’ effects of GR, may be protective after both myocardial infarction (123) and cerebral ischaemia (124) in mice. Similarly, glucocorticoids may reduce tissue damage during cardiopulmonary bypass (125), coronary ischaemia (126) and renal ischaemia (127). On the other hand, glucocorticoids may limit tetrahydrobiopterin availability as cofactor for nitric oxide synthesis (128), potentially promoting synthesis of damaging reactive oxygen species rather than protective nitric oxide (129, 130). Glucocorticoids may also adversely influence longer term remodelling of the myocardium following infarction. MR-mediated fibrosis in the myocardium has received a great deal of attention since the randomised Aldactone evaluation study (RALES) and Eplerenone post acute myocardial infarction heart failure efficacy and survival study (EPHESUS) studies demonstrated the benefits of MR antagonists in patients with heart failure (131, 132). Although 11β-HSD2 has been described in human heart (72–75), its cellular distribution and magnitude of activity remain uncertain: it is likely to be insufficient to exclude cortisol from access to MR. Therefore, it may be cortisol rather than aldosterone which occupies MR in the myocardium (Fig. 1A) and influences fibrotic responses (133). In addition, GR activation prevents angiogenesis (86, 134, 135), a key process in the recovery from infarction which ensures collateral circulation and reperfusion. Administration of glucocorticoids beyond the first few days after infarction might be predicted to impair reperfusion.

A number of clinical trials have been undertaken to test the effects of glucocorticoids administered in the first few days after myocardial infarction. Most of these were conducted in the 1970s with suboptimal methodology, but a recent meta-analysis suggests a small beneficial effect on mortality (136). The increased incidence of heart failure amongst glucocorticoid users in the pharmacoepidemiology studies described above (99, 100, 137), however, raises the possibility that longer term glucocorticoid therapy has an adverse effect on vascular remodelling.

While anti-angiogenic therapy may have a role in oncology and in treating ischaemic retinopathies, pro-angiogenic therapy has been sought to improve collateral revascularisation following ischaemia and infarction. Since glucocorticoids inhibit angiogenesis and 11β-HSD1 regenerates glucocorticoids within blood vessels, we recently tested the hypothesis that loss of 11β-HSD1 would enhance angiogenesis (86). We found that 11β-HSD1 null mice exhibit enhanced angiogenesis in isolated aortic rings, in sponges inserted subcutaneously, in surgical wounds, and in the myocardium following coronary artery ligation and myocardial infarction. This was associated with improved recovery from infarction as judged by left ventricular ejection fraction (Fig. 4).

**Recovery from intravascular injury**

One of the reasons for improved survival from cardiovascular disease is the advent of intravascular...
interventions, including balloon angioplasty (1). A major limiting factor following such procedures, however, is the occurrence of early restenosis in which vascular smooth muscle neo-intimal proliferation is prominent. Similar pathological processes may also be relevant in the spontaneous formation of occlusive plaques. On the basis that glucocorticoids are anti-inflammatory and have anti-proliferative (138–140) and anti-migratory (141) effects on smooth muscle cells, they have been employed to prevent restenosis (16, 142). Systemic administration was effective in many animal models (reviewed in (16)). However, in clinical trials, glucocorticoids have been successful in some (143–146) but not all (147–151) studies. A likely explanation for discrepant results is that the benefits of local anti-inflammatory effects in the injured blood vessel are offset by adverse systemic effects. Alternatively, the observation that MR antagonists also reduce neo-intimal lesion formation (152) suggests that the anti-inflammatory effects of GR activation may be offset by pro-inflammatory MR activation (153). To overcome these limitations, glucocorticoid-eluting stents have been proposed to deliver local anti-inflammatory therapy (154–156) using glucocorticoids devoid of affinity for MR, such as dexamethasone and prednisolone (7). However, there remains the risk that GR may induce changes within the vessel which offset any benefit of conventional anti-inflammatory effects, for example by increasing local angiotensin II (157, 158) or endothelin-1 (159) generation or by decreasing endothelial nitric oxide generation (160).

Conclusions

The evidence reviewed above suggests that glucocorticoid excess not only induces cardiovascular risk factors, but also hastens the incidence and progression of atheromatous vascular disease. This probably reflects the combined effects of systemic and local vascular actions of glucocorticoids. Systemic effects are mediated through GR activation in liver, adipose tissue, pancreas and muscle; MR activation in kidney may also be involved in people with impaired 11β-HSD2 activity. Local effects in the blood vessel wall and myocardium are mediated by both GR and MR and modified in a cellspecific pattern by 11β-HSD1 and 11β-HSD2. These local effects may influence not only atherogenesis but also the outcomes of vascular occlusion and injury. They may be both protective (preventing neointimal proliferation via GR and promoting perivascular inflammation and myocardial fibrosis via MR). It is probable that cortisol is the principal ligand occupying MR in cardiovascular tissues, so that the focus on the renin–angiotensin–aldosterone axis in interpreting the clinical benefits of MR antagonists is arguably misplaced. In addition to MR antagonism, inhibition of 11β-HSD1 provides a route to prevent both MR and GR activation in many tissues including liver, adipose tissue and vascular smooth muscle. The net effect of 11β-HSD1 inhibition appears to be atheroprotective and beneficial after myocardial infarction in mice. These findings offer the promise of therapeutic potential for tissue-specific manipulation of glucocorticoid action in the prevention and treatment of cardiovascular disease in humans.

Acknowledgements

Our research is funded predominantly by the British Heart Foundation and the Wellcome Trust. The author is grateful to many co-authors, colleagues and collaborators for their invaluable contributions.

Disclosure

Within the past 2 years, B R W has consulted for AstraZeneca, Dainippon Sumitomo, Merck, Johnson & Johnson, Incyte, Ipsen, Roche, Vitae, Zydus Research Centre and received lecture fees from Abbott and Bristol Myers Squibb. B R W is an inventor on relevant patents held by University of Edinburgh.

References

3 Stewart PM & Krozerowski ZS. 11 Beta hydroxysteroid dehydrogenase. Vitamins and Hormones 1999 57 249–324.


Ullian ME. The role of corticosteroids in the regulation of vascular tone. Cardiovascular Research 1999 41 55–64.


Expression of the mRNA coding for 11β-hydroxysteroid dehydrogenase type 1 in adipose tissue from obese patients.

Interaction between an 11β-hydroxysteroid dehydrogenase type 1 gene variant and birth era

Vascular localization of the 11β-hydroxysteroid dehydrogenase type II enzyme.

Selective inhibition of 11β-hydroxysteroid dehydrogenase type 1 improves hepatic insulin sensitivity in hyperglycaemic mice strains.

Selective inhibition of 11β-hydroxysteroid dehydrogenase type 1 decreases blood glucose concentrations in hyperglycaemic mice.

Selective inhibition of 11β-hydroxysteroid dehydrogenase type 2 and effects on responses to glucocorticoids in vitro.

Glucocorticoids promote non-piogenic phagocyte clearance of apoptotic leucocytes.

Glucocorticoids and cardiovascular disease

www.eje-online.org
dehydrogenase type 1 promotes macrophage phagocytosis of apoptotic leukocytes. *Journal of Immunology* 2006 176 7605–7611.


104 Maradit KH, Reinolda MS, Crowson CS, Davis JM, III, Hunder GG & Gabriel SE. Glucocorticoids and cardiovascular and cerebrovascular events in polymyalgia rheumatica. *Arthritis and Rheumatism* 2007 57 279–286.


Glucocorticoids and cardiovascular disease


122 Alisky JM. Dexamethasone could improve myocardial infarction outcomes and provide new therapeutic options for non-interventional patients. *Medical Hypotheses* 2006 **67** 53–56.


146 Ferrero V, Ribichini F, Rognoni A, Marino P, Brunelleschi S & Vassanelli C. Comparison of efficacy and safety of lower-dose to


Received 10 July 2007
Accepted 20 August 2007