

Cardiovascular consequences of cortisol excess

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Abstract: Cushing's syndrome is a consequence of primary or, more commonly, secondary oversecretion of cortisol. Cardiovascular disease is the major cause of morbidity and mortality in Cushing's syndrome, and excess risk remains even in effectively treated patients. The cardiovascular consequences of cortisol excess are protean and include, inter alia, elevation of blood pressure, truncal obesity, hyperinsulinemia, hyperglycemia, insulin resistance, and dyslipidemia. This review analyses the relationship of cortisol excess, both locally and at tissue level, to these cardiovascular risk factors, and to putative mechanisms for hypertension. Previous studies have examined correlations between cortisol, blood pressure, and other parameters in the general population and in Cushing's syndrome. This review also details changes induced by short-term cortisol administration in normotensive healthy men.

Keywords: blood pressure, cortisol, Cushing's syndrome, risk factors

Introduction

Cortisol, the major human glucocorticoid, is essential for maintenance of normal blood pressure and in excess, either general or local, produces hypertension (Kelly, Mangos, et al 1998). Naturally occurring glucocorticoid hypertension in its most florid form, Cushing's syndrome, is rare. It is estimated to affect 1 in 300–400 hypertensives in referral centres, and around 5–25 per million of the general population. Iatrogenic Cushing's syndrome, on the other hand, is common. Widely used clinically, synthetic glucocorticoids are said to cause hypertension in some 20% of patients, but steroids invariably raise blood pressure in experimental studies (Whitworth et al 1989). There is considerable interest in the notion that cortisol may play a role in some forms of essential hypertension and it has been suggested that cortisol may contribute to around 30% of all cases of hypertension (Walker et al 1991; Soro et al 1995; Mangos, Kelly, et al 2000). There is interest in the role of cortisol in determination of cardiovascular risk (Walker et al 1998; Fraser et al 1999; Girod et al 2004).

We have previously examined hemodynamic, volume, metabolic, and hormonal effects of cortisol in a series of studies which have defined the characteristics of cortisol-induced hypertension in normotensive healthy men (Whitworth, Saines, et al 1984; Connell et al 1987; Pirpiris et al 1993; Wong et al 1993; Whitworth et al 1994, 1994a, 1994b; Williamson et al 1996; Tam, Kelly, et al 1997; Tam, Williamson, et al 1997; Kelly, Tam, et al 1998; Macefield et al 1998). In this review, we discuss changes in cardiovascular risk factors produced by cortisol and factors which might contribute to the blood pressure rise. There is a large range of literature on effects of synthetic glucocorticoids, such as prednisolone and dexamethasone, but this review is confined to consideration of the major naturally occurring adrenocorticosteroid

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hormone, cortisol. The effect of the synthetic steroid dexamethasone on cardiovascular biomarkers has been delineated recently by Brotman, Girod, et al (2005).

Cardiovascular risk factors

Excess cardiovascular morbidity and mortality is a feature of Cushing's syndrome (Etxabe and Vazquez 1994). Untreated Cushing's syndrome has a poor prognosis, with only a 50% 5-year survival. Even in treated Cushing's syndrome, morbidity remains high, with a very substantial contribution from cardiovascular disease (Ross and Linch 1982; Etxabe and Vazquez 1994; Colao et al 1999). In subclinical Cushing's syndrome, both systolic and diastolic blood pressures were significantly elevated compared with controls due to incidentally discovered adrenal adenoma with mild autonomous cortisol hyperproduction (Tauchmanova et al 2002). Patients treated with glucocorticoids also have significantly increased risk of cardiovascular and cerebrovascular disease (Souverein et al 2004; Wei et al 2004).

Hypertension

There is good evidence that the elevated blood pressure seen in Cushing's syndrome is a consequence of adrenocorticotrophic hormone (ACTH) stimulated increases in cortisol secretion. We have shown that ACTH reproducibly increases blood pressure in both healthy normotensive and hypertensive subjects, but not in patients with Addison's disease on steroid replacement. This indicates ACTH hypertension is adrenally dependent (Whitworth et al 1983). We subsequently showed that the blood pressure raising effects of ACTH were reproduced by cortisol infusion appropriate for conditions of ACTH stimulated cortisol secretion (Whitworth, Saines, et al 1984). Although ACTH receptors have been demonstrated in human aortic endothelial cells (Hatakeyama et al 2000), it seems unlikely that direct actions of ACTH are involved in ACTH hypertension in humans. Cortisol excess was correlated with the hypertension in Cushing's syndrome in a case report (Suzuki et al 1992), and in 28 patients (Soszynski et al 1991), but not in all studies (Sonino et al 1992). There is no relationship between mineralocorticoid excess and hypertension, and no difference between concentrations of other adrenocortical steroids in Cushing's syndrome and essential hypertension (Whitworth et al 2004). Spironolactone, a mineralocorticoid antagonist, did not significantly lower blood pressure in patients with Cushing's syndrome (Saruta 1996). These

observations, together with experimental studies using cortisol, indicate that cortisol is very likely the responsible steroid in the hypertension of Cushing's syndrome. Hypertension was a feature of 9/12 of Cushing's original cases (Danese and Aron 1994) and is found in around 80% of cases (Plotz et al 1952). We have shown that administration of cortisol to normotensive healthy men reproducibly raises blood pressure (Whitworth, Saines, et al 1984; Connell et al 1987; Whitworth et al 1994, 1994a, 1994b; Williamson et al 1996). The increase in plasma cortisol concentration produced by cortisol at 200 mg/day was associated with a highly significant rise in systolic blood pressure (Table 1).

There is some evidence that cortisol excess may be a feature of essential hypertension. Litchfield and colleagues (1998) found higher urinary free cortisol excretion in 153 white patients with essential hypertension than 18 normotensive controls. The authors of the Four Corners Study (Watt et al 1992) observed higher plasma cortisol concentrations in 50 young people with high blood pressure and high parental blood pressure compared with similar numbers of people with lower pressure. Morning plasma cortisol concentrations were elevated in untreated male hypertensives selected from the Paris Prospective Study (total cohort n = 6424) (Filipovsky et al 1996). Systolic blood pressure was related to fasting plasma cortisol concentration

Table 1 Effects on cardiovascular risk factors of cortisol administration (200 mg/day) for 5 days in normotensive healthy men

Parameter	n	Control	Cortisol	p
Plasma cortisol (nmol/L)	33	402 ± 21	1045 ± 73	<0.001
Systolic blood pressure (mmHg)	33	117 ± 1	129 ± 1	<0.001
Body weight (kg)	8	70.4 ± 2.8	71.4 ± 2.8	<0.001
Fasting plasma glucose (mmol/L)	46	4.1 ± 0.1	5.0 ± 0.2	<0.001
Plasma insulin (mU/L)	11	16 ± 2.1	22.8 ± 2.1	0.05
HOMA	11	1.25 ± 0.18	1.44 ± 0.14	ns
Plasma cholesterol (mmol/L)	10	4.3 ± 0.3	4.3 ± 0.3	ns
HDL (mmol/L)	10	1.1 ± 0.1	1.3 ± 0.1	ns
LDL (mmol/L)	10	2.7 ± 0.3	2.6 ± 0.3	ns
Plasma triglycerides (mmol/L)	10	1.2 ± 0.9	1.1 ± 0.5	ns
Plasma homocysteine (µmol/L)	6	9.32 ± 0.87	9.72 ± 0.85	ns
Plasma urate (mmol/L)	6	0.37 ± 0.03	0.28 ± 0.01	0.015
Plasma vitamin C (µmol/L)	6	29.0 ± 6.7	27.0 ± 4.7	ns
Plasma vitamin E (µmol/L)	6	24.0 ± 0.7	21.2 ± 2.1	ns
Plasma t-PA (ng/ml)	6	8.6 ± 0.7	7.4 ± 0.8	0.025
Plasma PA-I (ng/ml)	8	6.2 ± 1.3	3.6 ± 1.3	ns
Corrected serum calcium (mmol/L)	8	2.33 ± 0.02	2.32 ± 0.01	ns

NOTE: Results shown as mean ± s.e.m.

Abbreviations: n, number of subjects; HOMA, homeostasis model assessment score; HDL, high density lipoproteins; LDL, low density lipoproteins; ns, nonsignificant; t-PA, tissue plasminogen activator; PA-I, plasminogen activator inhibitor -I

in a cohort of 370 English men (Phillips et al 1998), but Fraser et al (1999) found no correlation of cortisol excretion rate with blood pressure in 439 normal Scots. Walker et al (2000) examined 226 Swedish subjects in a cross-sectional study and found higher plasma cortisol was independently associated with higher diastolic blood pressure in men, but not women. In another study of 593 English subjects, higher cortisol under the curve during oral glucose tolerance testing was associated with higher systolic blood pressure (Reynolds et al 2003). In an Indian cohort of 509 subjects, 9 am cortisol was strongly associated with systolic and diastolic blood pressure (Ward et al 2003). Sensitivity to glucocorticoids was also increased in 11 patients with essential hypertension compared with matched normotensive controls (Walker et al 1996).

Phillips (2004) has reviewed evidence for the concept of fetal programming of the neuroendocrine response to stress and the association of increased adrenocortical and sympathoadrenal responses with small size at birth.

The observation that peroxisome proliferator-activated receptor agonists lower blood pressure in humans (Hirose et al 2002) is of interest in this regard given their observed effects on downregulation of 11 beta-hydroxysteroid dehydrogenase 1 (11 β -HSD1), and hence availability of biologically active glucocorticoids (Berger et al 2001).

Obesity

Truncal obesity is a hallmark of Cushing's syndrome. Patients with Cushing's disease (n=25) had higher body mass index and waist to hip ratio than age and sex matched controls (Faggiano et al 2003). These features persisted in 15 patients who had been cured over 5 years previously (Colao et al 1999). In our studies of short-term cortisol administration (200 mg/day) in normotensive healthy men, weight gain is a feature (Table 1) and most likely represents salt and water retention over the 5-day period (Connell et al 1987) (see below).

Cortisol excretion rate correlated positively with body mass index and waist and hip measurements in both men and women in a general Scottish population (n=439), with the relationship persisting in men after multiple regression analysis (Fraser et al 1999). A rise of morning salivary cortisol correlated with body mass index, waist-hip ratio, and abdominal sagittal diameter in 28 Swedish men (Wallerius et al 2003). As discussed by Fraser et al (1999), the majority of, but not all, studies (Stolk et al 1996) found a correlation of urinary cortisol excretion with measures of

obesity. Although cortisol excretion was increased, circulating cortisol was not high in most subjects. Indeed, although cortisol secretion is elevated, circulating concentrations may be normal or low (Bjorntorp and Rosmond 2000). Stolk and colleagues (1996) speculated that the clear effects of cortisol hypersecretion on body fat as compared with the difficulty in identifying the relationship in normal subjects may reflect differences in potency of cortisol at the target tissue level. In this context, Bujalska et al (1997) suggested central obesity may reflect "Cushing's disease of the omentum". They found adipose stromal cells from omental, but not subcutaneous fat, can generate active cortisol from inactive cortisone through expression of 11 β -HSDI, and that enzyme expression was increased after exposure to cortisol and insulin. They concluded that in vivo, such a mechanism would ensure constant glucocorticoid exposure specifically to omental fat, leading to central obesity (Bujalska et al 1997). This group has subsequently shown that in intact undifferentiated omental adipose stromal cells, 11 β -HSDI acts primarily as a dehydrogenase, but in mature cells oxoreductase activity dominates. They postulated that as glucocorticoids inhibit cell proliferation, 11 β -HSDI activity in uncommitted cells may facilitate proliferation, but once early differentiation is initiated, a switch to oxoreductase activity generates cortisol, promoting adipogenesis (Bujalska et al 2002). Whorwood and colleagues (2001, 2002) have speculated that regulation of glucocorticoid receptor isoforms and 11 β -HSDI expression in skeletal muscle may play a key role in insulin resistance and that increased receptor expression may contribute to pathogenesis of the metabolic syndrome.

Hyperglycemia

Glucose intolerance and diabetes mellitus are very common in Cushing's syndrome. Fasting glucose was significantly higher in patients with Cushing's than those in remission (Terzolo et al 2004), and in patients (n=25) than age and sex matched controls (Faggiano et al 2003). Elevated fasting glucose is also a feature of subclinical Cushing's syndrome (Tauchmanova et al 2002). Fasting plasma glucose elevation is a common accompaniment of cortisol administration. In our studies, fasting plasma glucose rose consistently in normotensives after 5 days of cortisol administration (Table 1).

Both fasting and 2-hour stimulated plasma glucose concentrations correlated with 9 am fasting plasma cortisol in the cohort of 370 healthy men born in the UK between

1920 and 1930 studied by Phillips et al (1998). Walker et al (1998) found increased dermal sensitivity to glucocorticoid correlated with hyperglycemia as well as with hypertension and insulin resistance in 137 men. Wallerius et al (2003) reported a rise in morning salivary cortisol correlated with glucose in 28 Swedish men. In a large study from England (n=593), Reynolds et al (2003) found plasma cortisol and obesity had independent effects on plasma glucose (although independence should not be interpreted as causality [Brotman, Walker, et al 2005]). In a healthy South Asian cohort from Mysore (n=509), fasting glucose was strongly associated with 9 am plasma cortisol (Ward et al 2003). In patients with glucose intolerance, Andrews et al (2002) reported that cortisol secretion, although normal, is inappropriately high given enhanced peripheral sensitivity to glucocorticoids.

Insulin resistance

Insulin resistance is a feature of cortisol excess, both in clinical (Tauchmanova et al 2002; Faggiano et al 2003) and experimental settings (Connell et al 1987). Elevated insulin persists 5 years after cure of Cushing's disease (Colao et al 1999). Short-term cortisol administration in our studies of healthy men produced a significant increase in plasma insulin concentration but the homeostasis model assessment score, a measure of insulin resistance, was not significantly increased (Table 1).

The relationship between glucocorticoids and insulin resistance has been reviewed by Andrews and Walker (1999). Phillips et al (1998) examined the relationships between size at birth, plasma cortisol concentrations, and components of the insulin resistance syndrome in a cohort of 370 healthy English men born between 1920–1930. Fasting plasma cortisol concentrations were related to systolic blood pressure; plasma glucose: both fasting and 2 hours after an oral glucose tolerance test; plasma triglycerides; and insulin resistance. However, in 151 elderly Finnish women, 24-hour salivary cortisol did not correlate with the metabolic syndrome or birth size (Kajantie et al 2004).

A positive correlation between morning plasma cortisol concentration and fasting insulin concentration has been reported in healthy elderly Dutch women (Stolk et al 1996). In a Finnish study of 71 healthy men, the insulin resistance and hyperinsulinemia of centrally obese subjects was associated with increased urinary cortisol excretion, but circulating cortisol levels were low (Hautanen et al 1997). Wallerius et al (2003) found a positive association of a rise

in morning salivary cortisol with insulin concentration, and Ward et al (2003) found a positive association between 9 am cortisol and insulin resistance in a healthy South Asian population (n=509) born in Mysore between 1934–1954. Walker et al (1998) found increased dermal glucocorticoid sensitivity is associated with relative hypertension, insulin resistance, and hyperglycemia in men, including those with a genetic predisposition to hypertension.

Reynolds and colleagues (2002) examined skeletal muscle biopsies from 23 men without fasting hyperglycemia from the Uppsala Longitudinal Study of Adult Men. After adjusting for body mass index, higher levels of skeletal muscle glucocorticoid receptor messenger ribonucleic acid (mRNA) were associated with insulin resistance and with hypertension, but not plasma lipids, glucose, or body mass index alone. They suggested tissue specific variations in glucocorticoid receptor expression and function might provide insights into the pathophysiology of insulin resistance and its association with hypertension (Reynolds et al 2002). Evidence for the role of neuroendocrine stress in genesis of the metabolic syndrome comes from the work of Brunner and colleagues (2002) who found 24-hour cortisol metabolite and normetanephrine outputs were higher among cases (n=30) than controls (n=153) drawn from the Whitehall II cohort of middle aged working men.

Hyperlipidemia

Hyperlipidemia is said to be common in Cushing's syndrome with hypercholesterolemia and hypertriglyceridemia being prominent (Nashel 1986). In 25 Italian patients with Cushing's, high density lipoprotein (HDL) cholesterol was lower and low density lipoprotein (LDL) cholesterol higher than in matched controls (Faggiano et al 2003). However, neither total cholesterol nor HDL cholesterol were elevated in Cushing's syndrome compared with controls in another study of 41 Italians with active Cushing's syndrome (Terzolo et al 2004). Total cholesterol and triglycerides were elevated in 28 patients in Italy with subclinical Cushing's syndrome (Tauchmanova et al 2002). In 15 subjects who had had Cushing's disease cured over 5 years previously, total and LDL cholesterol and lipoprotein (a) concentrations remained higher than in 30 Italian controls (Colao et al 1999). In 10 normotensive healthy men we found 5 days' cortisol treatment did not alter plasma cholesterol, triglycerides, HDL, or LDL concentrations (Table 1). These data suggest that more prolonged periods of cortisol excess are required to produce dyslipidemia.

In a general Scottish population (n=439), Fraser and colleagues (1999) found cortisol excretion rate correlated negatively with HDL cholesterol and this correlation remained after multiple regression analysis. In a study of 226 Swedes, Walker et al (2000) found higher plasma cortisol associated with higher triglycerides in women, but not in men. In 28 Swedish men, a rise in morning salivary cortisol correlated with triglycerides (Wallerius et al 2003), and in 509 South Asians, 9 am cortisol was strongly associated with triglyceride concentration (Ward et al 2003).

Other risk factors

Hyperhomocysteinemia and lower folate concentrations have been reported in 41 Italian patients with Cushing's syndrome and homocysteine levels were significantly associated with midnight serum cortisol and serum folate (Terzolo et al 2004). Folate concentrations were all within the normal range in Cushing's syndrome, but homocysteine was elevated. Patients in remission were comparable with controls and the lower folates (4.9 ± 2.8 Cushing's, $7.2 \pm 2.8 \mu\text{mol/L}$ control) did not fully account for the increase in homocysteine levels (17.8 ± 4.1 Cushing's, $12.3 \pm 4.2 \mu\text{mol/L}$ control) which related to serum cortisol (Terzolo et al 2004). These same workers reported no differences in fibrinogen concentrations, but prothrombin time was higher and activated partial thromboplastin time lower in Cushing's than controls, albeit within the normal range. We found no effect of cortisol on plasma homocysteine concentrations in 6 normotensive healthy men. Plasma urate was decreased, and vitamin C and vitamin E were unchanged. There was a small fall in tissue plasminogen activator, but not in plasminogen activator inhibitor-1 (Table 1).

Faggiano et al (2003) found higher carotid intimamedia thickness and lower systolic lumen diameter and distensibility coefficient in 25 patients with Cushing's disease than controls. Artherosclerotic plaques were found in over 30% of patients. Plaques and carotid intimamedia thickness were also elevated in subclinical Cushing's syndrome, as was plasma fibrinogen (Tauchmanova et al 2002).

The Norwegian Tromsø study of 460 men and 486 women suggested serum calcium may be a predictor of cardiovascular disease in men (Jorde et al 1999). In epidemiologic studies, calcium correlates positively with blood pressure, blood glucose, and serum cholesterol. In

our studies of 5 days' cortisol administration, corrected plasma calcium was unchanged (Table 1).

Mechanisms of cortisol-induced hypertension Hemodynamics

Both cardiac output and peripheral resistance have been reported to be elevated in Cushing's syndrome (Agest et al 1974). Administration of cortisol to normotensive healthy subjects over 5 days leads to elevation of blood pressure, particularly systolic and mean, but also diastolic pressure in some studies, in association with significant increase in cardiac output, but no change in calculated total peripheral resistance (Connell et al 1987; Pirpiris et al 1993). Renal vascular resistance is elevated (Connell et al 1987). The rise in cardiac output may reflect the concomitant rise in plasma volume (Connell et al 1987), but it is not essential for development of hypertension. Pretreatment with the β -blocker atenolol prevented the rise in cardiac output, but did not prevent the rise in blood pressure, which in this case was associated with a rise in peripheral resistance (Pirpiris et al 1993). Conversely, the calcium channel blocker felodipine, which reduces peripheral resistance, had no effect on the rise in blood pressure produced by cortisol, which, in this case, was associated with increased cardiac output (Whitworth et al 1994). Cortisol-induced hypertension is normally associated with an increase in cardiac output, but the latter is not essential for a blood pressure rise, which can be mediated either by output, or by resistance.

Volume

Plasma volume is said to be increased, but total exchangeable sodium was normal in 11 patients with Cushing's disease and not correlated with hypertension (Ritchie et al 1990). Plasma volume, extracellular fluid volume (ECFV), and exchangeable sodium are all increased by cortisol in healthy normotensive subjects (Connell et al 1987). The increase in extracellular fluid volume is unlikely to be essential for the blood pressure rise as sodium restriction completely prevented the rise in ECFV produced by ACTH without abolishing the rise in blood pressure (Connell et al 1988). Adrenocorticotrophic hormone hypertension is explicable solely in terms of increased cortisol secretion (Whitworth, Saines, et al 1984). Sodium restriction substantially reduced the rise in exchangeable sodium, but did not modify the rise in plasma volume. However, these factors are unlikely

to be critical for cortisol-induced hypertension as the mineralocorticoid antagonist spironolactone, which blocks the sodium retention produced by cortisol, does not prevent the rise in blood pressure (Williamson et al 1996). Further, synthetic glucocorticoids, which are natriuretic, produce elevations of blood pressure without any urinary sodium retention or increase in body weight or plasma volume (Whitworth et al 1989). Cortisol-induced hypertension is not simply explained by mineralocorticoid-induced salt and water retention.

Sympathetic nervous system

Plasma and urine catecholamine concentrations were normal in Cushing's disease ($n=11$), but cardiac sensitivity to the β -receptor agonist isoprenaline was increased, without increased β -receptor density (Ritchie et al 1990). In cortisol-treated normotensive healthy subjects measures of sympathetic nervous activity, including plasma catechols (Connell et al 1987), resting noradrenaline spillover rate (Pirpiris et al 1992), reflex sympathetic function, (cold pressor, hand grip, mental arithmetic) (Tam, Kelly, et al 1997), and neuropeptide Y concentrations (Whitworth et al 1994a) were unchanged. Muscle sympathetic vasoconstrictor activity measured directly from peroneal nerve recordings was decreased by cortisol (Macefield et al 1998). Hypertension was amplified, not abolished, by autonomic blockade (Tam, Williamson, et al 1997). Cortisol-induced hypertension cannot be ascribed to sympathetic nervous system overactivity. Pressor responsiveness to catechols is increased by cortisol treatment (Pirpiris et al 1992). This may be, at least in part, a consequence of suppression of sympathetic nervous activity.

Vasopressor hormones

Cortisol has a range of effects on the renin-angiotensin system. Renin substrate (angiotensinogen) may be increased in Cushing's syndrome, but renin and angiotensin are usually normal (Tenschert et al 1985; Ritchie et al 1990). Therapy with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists has variable effects (Vetter et al 1976; Saruta et al 1986). Pressor responsiveness to angiotensin II is increased (Saruta et al 1986). In cortisol treated normal subjects, plasma renin and angiotensin II concentrations were decreased (Connell et al 1987). Angiotensin II pressor responsiveness was moderately increased (Whitworth et al 1988) and this is likely to be explained, at least in part, by decreased plasma concentration

of angiotensin II leading to upregulation of angiotensin receptors. The well recognised glucocorticoid stimulated increase in angiotensinogen does not lead to increased plasma angiotensin II concentrations, and it is unlikely to be a key causal mechanism in human glucocorticoid hypertension.

In an Italian study of Cushing's disease, vasopressin (AVP) was higher in 13 hypertensives than 11 normotensives and surgical treatment reduced AVP (Giuditta et al 2004). We did not observe any alteration in plasma AVP concentrations in cortisol-treated normotensive healthy men (Connell et al 1987). Thromboxane has been reported to correlate with cortisol concentrations in both healthy subjects ($n=19$) and those at high cardiovascular risk ($n=31$) (Fimognari et al 1996), but information in other conditions is limited. Plasma endothelin concentrations are elevated in Cushing's syndrome ($n=13$), but did not correlate with blood pressure, plasma cortisol levels, or urinary cortisol excretion (Kirilov et al 2003). In 9 normotensive healthy men treated with cortisol we observed a nonsignificant rise in urine endothelin excretion after 5 days (Table 2). The role of insulin as a mediator of hypertension has been the subject of much research. We observed rises in blood pressure and plasma glucose and insulin concentrations in normotensives treated with cortisol, but treatment with the somatostatin analogue octreotide, which reversed the rise in insulin, had no effect on blood pressure, which suggests the two factors are not causally related (Whitworth et al 1994b).

Table 2 Effects on vasoactive hormones of cortisol administration (200 mg/day) for 5 days in normotensive healthy men

Parameter	n	Control	Cortisol	p
APRC (pmol AI/ml/h)	16	5.0 ± 0.72	0.7 ± 0.09	<0.001
Urine endothelin excretion (ng/day)	9	39 ± 7	52 ± 14	ns
Urine 6 keto PGF 1 α /Cr (ng/mmol)	9	45 ± 7	36 ± 5	ns
Urine 2, 3 dinor 6 keto PGFI α /Cr (ng/mmol)	9	353 ± 41	462 ± 73	0.039
Urine cGMP (nmol/day)	9	522 ± 51	911 ± 961	0.004

NOTE: Results shown as mean \pm s.e.m.

Abbreviations: APRC, active plasma renin concentration; PG, prostaglandin; Cr, creatinine; cGMP, cyclic guanosine monophosphate; ns, nonsignificant.

Vasodilator hormones

Cushing's syndrome is reported to be associated with reduced activity of the kallikrein-kinin system and prostaglandins (Saruta 1996), but in another study kinin system components were higher (Shimamoto et al 1995). Urinary kallikrein activity rose in healthy subjects treated with cortisol (Whitworth, van Leeuwen, et al 1984). Atrial natriuretic peptide is increased in Cushing's syndrome (Yamaji et al 1988) as it is by cortisol treatment in normal subjects (Connell et al 1987). Accordingly there is no evidence to suggest atrial natriuretic peptide deficiency is important in the aetiology of the hypertension.

We have measured urinary prostanoids in 9 cortisol-treated normotensive subjects: 6 keto prostaglandin (PG) FI α /creatinine ratio (ng/mmol) was not significantly changed; and 2, 3 dinor 6 keto PG FI α /creatinine (ng/mmol) rose (Table 2). These studies provide no evidence for vasodilator prostanoid deficiency. Urinary cyclic guanosine monophosphate was also increased (Table 2). In another study, the cyclooxygenase inhibitor indomethacin did not modify the magnitude of changes in pressor responsiveness to phenylephrine or angiotensin II produced by cortisol (Whitworth et al 1988).

Saruta (1996) reported low urinary excretion of reactive nitrogen intermediates (a marker of vasodilator nitric oxide activity) in a patient with Cushing's syndrome, even after L-arginine administration. In healthy men on a low nitrate diet, we demonstrated that cortisol administration was associated with a fall in plasma reactive nitrogen intermediates, but not in L-arginine or asymmetric dimethyl arginine concentrations (Kelly, Tam, et al 1998). L-arginine did not prevent cortisol-induced rises in blood pressure (Kelly et al 2001). Cortisol also inhibits cholinergic dilation in the forearm, similar in magnitude to the inhibition produced by nitric oxide synthase (Mangos, Walker, et al 2000). L-arginine transport is normal in cortisol-treated subjects (Chin-Dusting et al 2003). Inhibition of vasodilator nitric oxide is a strong candidate for the genesis of glucocorticoid hypertension (Kelly, Tam, et al 1998; Whitworth et al 2000).

Summary

There is increasing evidence that cortisol contributes to cardiovascular risk, not only in Cushing's syndrome, but more generally. Hypertension, truncal obesity, hyperglycemia, insulin resistance, and dyslipidemia are all important in this regard. Glucocorticoid hypertension is not

explicable in terms of mineralocorticoid-induced sodium retention and volume expansion. Inhibition of vasodilator nitric oxide is a strong candidate mechanism in the development of hypertension. Therapies should be aimed at lowering cardiovascular risk in patients with Cushing's syndrome, which will probably need to target multiple metabolic and hemodynamic abnormalities.

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