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Evidence for altered hypothalamus–pituitary–adrenal axis functioning in systemic hypertension: Blunted cortisol response to awakening and lower negative feedback sensitivity

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Summary
Background: Hypothalamus–pituitary–adrenal (HPA) axis functioning in systemic hypertension is not fully understood. We explored HPA axis activity and feedback sensitivity to oral administration of dexamethasone in systemic hypertension via assessment of the cortisol awakening response (CAR) and the circadian cortisol profile.
Methods: The CAR and circadian cortisol profile were assessed in 20 unmedicated and otherwise healthy middle-aged hypertensive men and in 22 normotensive male controls. Salivary free cortisol measures for the CAR were obtained immediately after awakening and 15, 30, 45, and 60 min thereafter. Circadian cortisol secretion was sampled at 08:00, 11:00, 15:00, and 20:00 h. Assessment of the CAR was repeated on the next day after administration of 0.5 mg dexamethasone at 23:00 h on the previous night.
Results: Hypertensives had a significantly lower CAR ($p<0.02$) and significantly reduced suppression of the CAR after dexamethasone administration ($p<0.01$) than normotensive controls. There were no significant differences in cortisol levels at awakening and in circadian cortisol profiles between hypertensives and normotensives.
Conclusion: We found evidence for altered HPA axis activity in men with systemic hypertension evident with the CAR. Hypertensives showed relative attenuation in the CAR

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and in the HPA axis feedback sensitivity following dexamethasone suppression. Such alterations in HPA axis regulation might contribute to the atherosclerotic risk in hypertensive individuals.

1. Introduction

The end-product of the hypothalamus–pituitary–adrenal (HPA) axis, the endogenous glucocorticoid cortisol has been associated with hypertension (al'Absi and Arnett, 2000). Cortisol has a ready access to the central nervous system (CNS) affecting areas of the brain amongst them parts of the limbic system crucially involved in the control of blood pressure (BP) regulation (Sapolsky et al., 2000; Ku, 2006). In addition to the brain, glucocorticoid receptors are present in the heart, and in the vascular smooth muscle of the resistance vessels, as well as in the kidney, thereby directly mediating the effect of cortisol on BP (Kenyon and Fraser, 1992). Whereas it is widely accepted that glucocorticoids can contribute to the development of hypertension (al'Absi and Arnett, 2000; Whitworth et al., 2000) findings on HPA activity in clinical hypertension are inconsistent. While some studies showed increased urinary excretion of cortisol metabolites in hypertensive and hypertension-prone individuals (Kornel et al., 1969; Soro et al., 1995; Litchfield et al., 1998; Walker et al., 1998) other investigations could not consistently demonstrate abnormalities in cortisol secretion or diurnal rhythm in patients with systemic hypertension (Whitworth et al., 1989; Walker, 1996; Wirtz et al., 2004). Circadian free cortisol profiles have not yet been reported in hypertensives compared to normotensives.

Recently, the cortisol awakening response (CAR) has been recognized as a distinct phenomenon in the diurnal cortisol output with considerable clinical significance (Wust et al., 2000; Clow et al., 2004; Williams et al., 2005; Esposito et al., 2006). The CAR is the change in cortisol concentration that typically takes place in the 20–45 min after waking up in the morning. The CAR is usually assessed with repeated saliva sampling during that time interval. It provides a simple and reliable means of assessing the dynamic activity of the HPA axis (Pruessner et al., 1997; Wessa et al., 2006). Of considerable interest with respect to the increased cardiovascular risk in hypertensive individuals (Kaplan, 1989), the salivary CAR, but not the 24-h urinary cortisol secretion have previously been associated with intermediate biological risk factors for cardiovascular disease (Rosmond and Bjorntorp, 2000; Eller et al., 2001). Reduced reactivity in saliva cortisol in the first hour after awakening was previously associated with higher degree of atherosclerosis as evidenced by greater intima media thickness (Eller et al., 2001). Similarly, a low morning cortisol peak has been associated with higher levels of traditional cardiovascular risk factors, including BP (Rosmond and Bjorntorp, 2000). Following this research, one might expect an attenuated CAR in hypertensive patients compared to normotensives, although this has not been studied.

Alterations in glucocorticoid sensitivity may cause differential cortisol production. Glucocorticoid sensitivity defines the extent to which target organs are responsive to a given amount of cortisol. A high GC sensitivity means that a biological system endows high propensity for cortisol effects and vice versa (Ebrecht et al., 2000). There is evidence that glucocorticoid sensitivity of different target tissues is altered in hypertension (Walker et al., 1996; Wirtz et al., 2004). One method to define glucocorticoid sensitivity in humans is the assessment of the negative feedback control of the HPA axis as determined by the magnitude of cortisol suppression after oral administration of dexamethasone (Ebrecht et al., 2000). While one earlier study found relatively more non-suppressors among hypertensives than among normotensives (Pfohl et al., 1991) another study did not find differences in cortisol secretion with dexamethasone suppression between hypertensives and normotensives (Whitworth et al., 1989). Noteworthy, both of these studies did not measure the effect of dexamethasone suppression on the CAR.

The objective of our study was to explore HPA activity and feedback sensitivity in a sample of unmedicated hypertensive and normotensive men. We measured salivary free cortisol responses to awakening and collected circadian cortisol profiles. The CAR was determined twice once with and once without the dexamethasone suppression test.

2. Materials and methods

2.1. Subjects

Participants of a research project on stress reactivity in systemic hypertension (Wirtz et al., 2006a, b) were asked to participate in the study. From this original sample, 20 hypertensive and 22 normotensive subjects also participated in this study which has been formally approved by the Ethics Committee of the State of Zurich, Switzerland.

With the aid of the Swiss Red Cross Zurich and by advertisement, we recruited non-smoking hypertensive and normotensive men who, other than having hypertension, were in excellent physical and mental health confirmed by an extensive health questionnaire (von Kanel et al., 2004) and telephone interview. Specific exclusion criteria, obtained by subjects' self-report, were: regular heavy exercise, alcohol and illicit drug abuse; any heart disease, varicosis or thrombotic diseases, elevated blood sugar and diabetes, elevated cholesterol, liver and renal diseases, chronic obstructive pulmonary disease, allergies and atopic diathesis, rheumatic diseases, and current infectious diseases. In addition, participants were included only if they reported taking no medication, either regularly or occasionally. If the personal or medication history was not conclusive, the subjects' primary care physician was contacted for clarification.