DIURNAL VARIATION OF PLASMA CORTISOL AND HOMOVANILLIC ACID IN HEALTHY SUBJECTS

J. A. Posener1,2,3,4, J. J. Schildkraut1,4, J. A. Samson2,4 and A. F. Schatzberg2,4,5

1Massachusetts Mental Health Center, 74 Fenwood Road, Boston, MA 02115, USA; 2McLean Hospital, 115 Mill Street, Belmont, MA 02178, USA; 3Division of Psychiatry, Brigham and Women’s Hospital, 75 Francis Street, Boston, MA 02115, USA; 4Harvard Medical School, Boston, Massachusetts, USA; 5Department of Psychiatry and Behavioral Science, Stanford University School of Medicine, Stanford, California, USA

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SUMMARY

We investigated the relationship between plasma levels of cortisol, the dopamine metabolite homovanillic acid (HVA) and norepinephrine in healthy human subjects. Plasma cortisol and HVA levels were measured at 0800h, and in an integrated sampling procedure involving samples every 15 min between 1300 and 1600h. Plasma norepinephrine was measured at 0800 and 1300h. Cortisol, HVA and norepinephrine indices did not show significant correlations with each other. Both cortisol and HVA showed significant decreases over time. Longitudinal Random Effects (LRE) models were used to test whether individual cortisol and HVA curves over time were correlated; significant correlations were not found with this procedure. While significant correlations between cortisol and catecholamine indices have been reported in depressed patients, our results do not suggest such correlations in healthy subjects.

Keywords—Glucocorticoids; Hydrocortisone; Dopamine; Homovanillic acid; Depression; Psychotic disorders.

INTRODUCTION

We have hypothesized that the development of psychotic symptoms in depression may be due to increased activity of mesolimbic or mesocortical dopaminergic systems stimulated by the hypothalamic–pituitary–adrenal (HPA) axis (Schatzberg et al., 1985). This hypothesis was suggested by evidence that psychotic depression is characterized simultaneously by hypercortisolemia and increased dopamine activity, that psychotically depressed patients respond poorly to tricyclic antidepressants unless a neuroleptic is added, and that various HPA axis-derived substances are able to increase the activity of central dopamine systems in experimental animals (see Posener et al. (1994)).

Much remains to be understood about the normal human physiology of interactions between the HPA axis and dopamine systems. Correlations between cortisol in plasma or cerebrospinal fluid and various indices of catecholamine activity other than HVA levels have
been found in depressed patients by several authors (Maes et al., 1991; Lu et al., 1986; Träskman et al., 1980). Our group has reported that urinary free cortisol levels are highly correlated with urinary levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in depressed patients but not in healthy controls (Rosenbaum et al., 1983). Mazure et al. (1987) reported a significant correlation between morning plasma cortisol and plasma HVA in 15 depressed patients. However, Syvälahti (1985) did not find a significant correlation between post-dexamethasone plasma cortisol and morning plasma HVA in 12 depressed patients, some of whom appeared to have been taking psychoactive medications.

We now report a study of the relationship between plasma levels of cortisol and HVA in healthy human subjects. These measures were obtained at 0800h and in an integrated sampling procedure involving samples every 15 min between 1300 and 1600h. Halbreich et al. (1985) have shown that mean cortisol levels obtained with this integrated sampling technique predict closely mean cortisol levels over 24 h. Additionally, we examined relationships of cortisol and HVA to plasma norepinephrine levels at 0800 and 1300h.

METHODS

Healthy volunteers recruited by institutional advertisement were given an interview involving a psychiatric history, the Structured Clinical Interview for DSM-III-R (SCID), and a family history based on Research Diagnostic Criteria (FH-RDC); a medical history was also taken and a physical examination conducted by a physician. Subjects were required to have no lifetime history of psychiatric disorders including substance use disorders, no history of Axis I disorders in first-degree relatives, no active medical problems, and no current medication use. To reduce extraneous influences on the HPA axis and on catecholamine levels, subjects abstained from alcohol for 1 week before beginning the protocol and for 3 days prior to the study had no citrus fruits or bananas and no more than three cups daily of caffeine-containing beverages. Subjects fasted until after the morning blood samples were obtained. Ten healthy volunteers, seven males and three females, aged 23–40 years, had blood drawn at 0800h by venipuncture for plasma levels of cortisol, HVA and catecholamines. Subjects then returned in the afternoon and had a heparin-locked intravenous needle inserted at 1300h, at which time blood was drawn through the IV for determination of the same indices. Subsequently, blood was drawn through the IV for cortisol and HVA levels at 15 min intervals until 1600h, at which time the IV was removed and the protocol completed. We also obtained 0800h levels of cortisol and HVA by venipuncture in another five subjects, three males and two females, aged 24–47 years, who met the same entry criteria as the other subjects; three of these five also had catecholamine determinations carried out on this sample. Cortisol determinations were performed by radioimmunoassay (Taylor et al., 1983) in the Endocrinology Laboratory of Brigham and Women’s Hospital; HVA and catecholamine determinations were carried out by high performance liquid chromatography following the methods of Chang et al. (1983) and Bouloux et al. (1985), respectively, in the Neuropsychopharmacology/Psychiatric Chemistry Laboratory of the Massachusetts Mental Health Center.

Longitudinal data were analyzed first using repeated measures analysis of variance (ANOVA). To characterize the relationship between cortisol and HVA patterns over time, Longitudinal Random Effects (LRE) models were used (Waterman et al., 1989). LRE models were fitted using four random effects (corresponding to random intercept, slope,
Fig. 1. Morning and afternoon plasma levels of cortisol and HVA.

quadratic and cubic time coefficients) to describe the course of HVA over time. The correlation of cortisol with HVA over time was then estimated by adding cortisol as a time-varying covariate to the model and testing for significance using the Wald statistic. Pearson coefficients were used to characterize correlations between variables at single time points.
RESULTS

We examined correlations between the following variables: 0800h, 1300h and mean afternoon (mean of 1300–1600h) cortisol; 0800h, 1300h and mean afternoon HVA; and 0800h and 1300h norepinephrine. No correlation between cortisol and HVA measures approached significance; nor did norepinephrine measures correlate with cortisol and HVA indices. To examine whether correlations involving afternoon cortisol and HVA indices were affected by the stress of inserting the IV at 1300h, we re-computed mean afternoon values excluding levels drawn prior to 1400h; results did not change with this procedure. Cortisol measured at 0800h did not correlate with afternoon cortisol, while 0800h HVA correlated at a trend level with afternoon HVA (r = .60, p < .10); 0800h and 1300h norepinephrine did correlate significantly (r = .80, p < .005). Plasma samples assayed for norepinephrine were also assayed for dopamine and epinephrine levels, but these latter indices were undetectable in almost every case and did not relate meaningfully to other measures.

Regarding changes in cortisol and HVA over time, mean ± SD cortisol declined from 14.1 ± 3.5 μg/dl at 0800h to 6.1 ± 2.1 μg/dl at 1600h. Repeated measures ANOVA demonstrated that this decrease was statistically significant (F = 4.97, p < .0001), with post-hoc Newman–Keuls tests showing that the 0800h level was significantly higher than all subsequent levels, and that early afternoon levels were significantly higher than the 1600h level. Similarly, mean ± SD HVA declined significantly from 11.3 ± 2.3 ng/ml at 0800h to 8.2 ± 2.0 ng/ml at 1600h (F = 4.77, p < .0001), with post-hoc Newman–Keuls tests showing that 0800h and 1300h levels were significantly higher than levels at 1445h or subsequently, while levels at 1315h and 1330h were also significantly higher than levels at 1545h and 1600h.

The LRE models did not demonstrate a significant correlation between the cortisol and HVA curves over time across subjects. To eliminate the confound of stress associated with IV insertion at 1300h, the LRE analysis was re-computed after excluding levels drawn from 1300h to 1345h; this procedure did not change the results. The conclusion of the LRE analyses is borne out by examination of the cortisol and HVA data for the individual subjects, as presented in Fig. 1. Cortisol and HVA curves appear parallel, and in fact show statistically significant correlations in four subjects (subjects 4, 5, 7 and 9), while the correlations are at trend significance level in two others (3 and 10), and non-significant in four subjects (1, 2, 6 and 8). When cortisol and HVA levels between 1300h and 1345h are excluded, the only change is that the two correlations at trend significance level become significant at the p < .05 level. There were no differences in age or sex distributions between subjects with significant and non-significant correlations.

DISCUSSION

This study provides basic descriptive information about the relationship between plasma cortisol and HVA levels in healthy human subjects. Our data do not show a statistically significant association between these indices measured in the morning or afternoon. We observed significant declines over the course of the day in both measures, and these observations are consistent with the well-known diurnal variation of cortisol and with existing data on the diurnal variation of plasma HVA (Doran et al., 1990). However, we were not able to demonstrate an association between the pattern of changes over time in
these two measures. Examination of cortisol and HVA levels over time in individual subjects showed that these measures were significantly correlated in four out of 10 individuals, and it may be productive for further research to investigate whether the association between these measures differs in particular subgroups. We did not observe associations between either principal variable (cortisol and HVA) and measures of plasma norepinephrine. The apparent lack of association between plasma cortisol and HVA in this study contrasts with the finding of a significant correlation between these variables in depressed patients by Mazure et al. (1987) and with the general observations of associations between cortisol and catecholamine indices in depression. Together, these data are consistent with the earlier report by our group that urinary cortisol and MHPG are correlated in depressed patients but not in controls (Rosenbaum et al., 1983). If our findings are valid, they suggest that there may be an underlying interaction between the HPA axis and dopamine systems but that this mechanism is not normally a limiting factor in determining activity of the systems. In contrast, when one system is activated, as may be the case in major depression, this regulatory interaction may become partially limiting in determining the activity of the other system.

Caution is indicated in drawing conclusions from the results of this study for a number of reasons. First, the small sample size limits the power of the study, and the conclusion that there is not an association between plasma cortisol and HVA levels should be considered tentative until the results are replicated with a larger number of healthy subjects. Second, there has been substantial controversy over the significance of plasma HVA (see Davis et al. (1991)). While it is clear that only a minority of HVA in plasma derives from central sources, there is considerable evidence that plasma HVA correlates with clinical variables related to the severity and course of psychotic disorders. Finally, it is important to note that we sampled only a small portion of the circadian period. The HPA axis and presumably dopamine systems have important variation over the full 24 h, and it is possible that an association between the circadian rhythms of these systems would be found if the full period were studied. We are currently pursuing this latter line of investigation.

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