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## **Some Common Genetic Variants May Moderate the Stress Response through the HPA Axis<sup>i</sup>**

One of the key responses to stress involves the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to the production of the steroid hormone cortisol in the adrenal cortex. Once released into the bloodstream, cortisol has widespread effects throughout the body, affecting metabolism, cell growth, the cardiovascular system, and the immune system. The net effect of these changes is to temporarily rebalance various systems in the body, minimizing some and maximizing others, in order to cope with the stress that is present.

In healthy individuals cortisol production is regulated by a negative feedback loop. Cortisol travels through the circulatory system back to the hypothalamus, which then makes adjustments to the chain of hormone signals (CRH & ACTH) that controls cortisol production. Chronic stress and traumatic events can lead to dysregulation of the HPA Axis, which results in abnormal levels of cortisol in the body. Because the long-term dysregulation of the HPA system has been tied to a range of physical and psychiatric diseases, bio-behavioral scientists are interested in understanding more completely both the regulation of cortisol production and the way that cortisol affects target tissues in the body.

Cortisol interacts with cells by binding to two receptors: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). (The GR is found in most tissues of the body, including most areas of the brain. In the kidney and other tissues the mineralocorticoid receptor (MR) binds to aldosterone during the regulation of sodium resorption, but the MR is also present in the hippocampal region of the brain, where it binds to cortisol.) These steroid-receptor complexes then interact with DNA to either initiate or to repress the transcription of specific genes, in order to regulate the synthesis of proteins that bring about physiological changes in response to stress.

The MR binds cortisol with 10 times the affinity of the GR. The MR therefore binds most of the cortisol in the brain at lower, non-stressed levels, regulating the basal activity of the HPA axis and controlling the onset of the stress response. As cortisol levels increase the GR becomes increasingly bound, reducing activity in the HPA axis and eventually ending the stress response.<sup>ii</sup>

The effects that glucocorticoids such as cortisol have on a cell are determined both by the level of steroid exposure and by the glucocorticoid sensitivity of the cell (i.e., the efficiency with which the steroid-receptor complex is able to turn on a particular gene). Recent work has determined that variants of the GR gene can affect a cell's sensitivity to glucocorticoids. These differences may partially explain the large degree of individual differences in HPA activity and GC sensitivity.

A study by Wüst et al. (2004)<sup>iii</sup> examined the effects that common GR gene polymorphisms have on ACTH and cortisol responses to the Trier Social Stress Test (TSST), as well as to pharmacological stimulation. On the first day of the study salivary cortisol was used to monitor response to a low-dose ACTH (Synacthen) stimulation test. On three following days (at one-week intervals) blood and saliva samples were collected



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before and after administration of the TSST. Saliva was analyzed for cortisol; blood was analyzed for ACTH. Following an overnight treatment with dexamethasone (a synthetic glucocorticoid), blood samples were taken early the morning of the fifth day and analyzed for ACTH and dexamethasone. Saliva samples were then collected throughout the day for measurement of cortisol. DNA from the blood of research participants was also analyzed to determine the relative numbers of three polymorphisms: *BcII* RFLP, N363S, and ER22/23EK. (Due to the low number of participants found to have the ER22/23EK polymorphism, this group was not included in the statistical analysis.)

These findings suggest that the genotypes 363S carrier and *BcII* GG have opposite effects on salivary cortisol (and possibly ACTH) responses to stress. The 363S carriers had significantly elevated cortisol reaction to the TSST (compared to the wild type genotype), while the *BcII* GG genotype was associated with a slightly diminished stress response. Baseline cortisol levels were not significantly different among the experimental groups. There were no significant differences found among the genotypes for the ACTH stimulation test, and 363S carriers showed a trend toward enhanced cortisol suppression during the dexamethasone suppression test.

A second paper by Wüst and colleagues<sup>iv</sup> looked at the effect of the MR gene variant 180V on the HPA response (ACTH and cortisol) to the TSST. In this cohort (subjected to the TSST on three separate days), salivary cortisol and cortisol and ACTH from plasma were measured.

The findings suggest that carriers of the 180V allele had significantly higher salivary and plasma cortisol responses to the TSST, compared to the MR180I homozygotes. No such difference was found for the ACTH response, however.

Theoretical and technical advances enable the exploration of the interactions that exist between genetic variation, environment, and neuroendocrine function. These studies illustrate the advantage of using a multi-level and multi-system approach that simultaneously examines various physiological and genetic factors.

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<sup>i</sup> The content of this article is based on Wüst, et al. (2004) and DeRijk, et al. (2006), cited below.

<sup>ii</sup> De Kloet, E.R., Oitzl, M.S., Joëls, M. (1999). Stress and cognition: Are corticosteroids good or bad guys? *Trends Neurosci*, 22, 422-26.

<sup>iii</sup> Wüst, S., van Rossum, F.C., Federenko, I.S., et al. (2004). Common polymorphisms in the glucocorticoid receptor gene are associated with adrenocortical responses to psychosocial stress. *J Clin Endocrin Metab*, 89(2), 565-73.

<sup>iv</sup> DeRijk, R.H., Wüst, S., Meijer, O.C., et al. (2006). A common polymorphism in the mineralocorticoid receptor modulates stress responsiveness. *J Clin Endocrin Metab*, 91(12), 5083-89.