



# Genetic Variants in Serotonin Transporter and Corticosteroid Receptor Systems Influence Acute Stress Response



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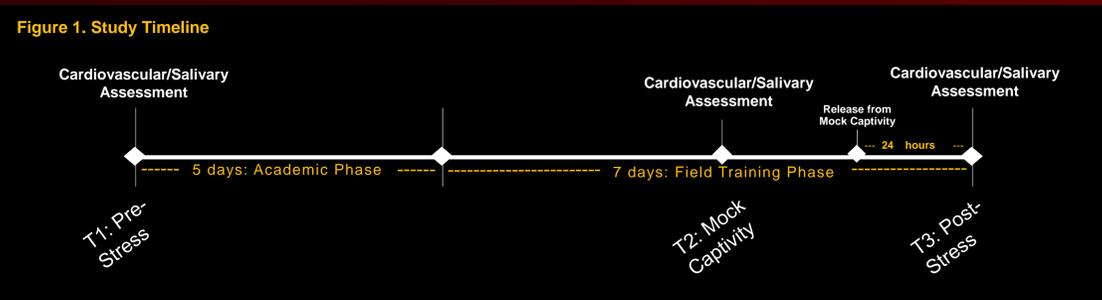
- ❖ This study revealed a remarkable synergistic effect of common polymorphisms on acute stress response in healthy males.
- ❖ 5HTTLPR SS carriers revealed higher overall cortisol concentrations than L carriers in response to intense, realistic stress.
- ❖ 5HTTLPR S carriers showed higher overall diastolic blood pressure (DBP) values than noncarriers (LL), Bcl1 GG were higher than C carriers, and -2C/G G carriers exceeded noncarriers (CC).
- ❖ A “high” genotype group revealed substantially higher overall cortisol concentrations than a “low” genotype group, as was the case for DBP.

## BACKGROUND & PURPOSE

- ◆ Repetitive responses to stress across the lifespan may precipitate psychosomatic and metabolic disease, though there is enormous individual variability in this relationship.<sup>1</sup> Therefore, it is crucial to understand individual differences in acute stress reactivity.
- ◆ Evidence suggests common variants in serotonin and corticosteroid receptor genes independently influence human stress reactivity, yet little is known of their combined effects, especially in high-stress environments.<sup>2-8</sup>
- ◆ The purpose of this study was to evaluate distinct and combined effects of polymorphisms in the serotonin transporter (5HTTLPR L/S), glucocorticoid receptor (Bcl1 C/G), and mineralocorticoid (-2C/G) receptor genes on adrenocortical and cardiovascular responses to intense, realistic stress in healthy male service members.

## METHODS

- ◆ **Participants:** 144 healthy, male military personnel attending military survival school (mean ± SD age = 25.2 ± 4.4 years).
- ◆ **Measures:** Cardiovascular and salivary assessments were performed at three time points: **T1**) first day of the academic phase of survival training, **T2**) directly after a stressful mock-captivity event, and **T3**) approximately 24 hours after release from mock captivity (see **Figure 1** for timeline).
  - ◆ **Cardiovascular measures:** Heart rate (HR) was collected via finger pulse oximeter; systolic blood pressure (SBP) and DBP were assessed via acoustic sphygmomanometer.
  - ◆ **Salivary sampling:** Saliva was collected using the passive drool technique; a modified Puregene (Gentra, QIAGEN Inc., Valencia, CA) extraction method was used to isolate DNA from the saliva samples, and gene-specific assays were conducted to identify genotypes.
- ◆ **Data Analysis:** Descriptive statistics, repeated measures Analysis of Covariance (ANCOVA); Bonferroni corrections were implemented for all comparisons at 0.5/3 = 0.017.
  - ◆ **High** and **low** genotype groups were constructed from polymorphisms that plausibly influenced each endpoint. High genotype group was constructed by summing constituent 5HTTLPR, Bcl1, and -2C/G genotypes as follows: cortisol [SS] + [CC] + [CC+CG]; HR [SS] + [GG+GC] + [CC+CG]; and DBP [SS+LS] + [GG] + [GG+GC]. Accordingly, low genotype group was constructed as follows: cortisol [LL+LS] + [GG+GC] + [GG]; HR [LL+LS] + [CC] + [GG]; and DBP [LL] + [CC+CG] + [CC].



## RESULTS

- ◆ Tests of a recessive model of the short variant of 5HTTLPR showed cortisol concentrations were significantly higher in SS than L carriers ( $F(1,133) = 5.4, p < 0.05, \eta_p^2 = 0.04$ ).
- ◆ HR recovery was superior in 5HTTLPR L carriers compared with short variant (SS) carriers (relative T2-T3Δ; -37.0% vs. -27.9%;  $t(135) = 3.3, p < 0.001$ ).
- ◆ DBP was influenced by all three polymorphisms:
  - ◆ 5HTTLPR S variant carriers (SS+SL) had higher DBP than noncarriers (LL;  $p < 0.05$ ).
  - ◆ For Bcl1 a recessive model for allele G showed higher DBP for GG carriers than C carriers (CC+GC;  $p < 0.05$ ).
  - ◆ For -2C/G, a dominant model for allele G showed higher DBP in G carriers (GG+GC) than CC ( $p < 0.05$ ).
- ◆ High ( $n = 8$ ) genotype group had significantly higher cortisol concentrations than low genotype group ( $n = 18$ ) at all three time points (**Figure 2**;  $F(1,24) = 18.4, p < 0.001, \eta_p^2 = 0.43$ ).
- ◆ High ( $n = 8$ ) genotype group had significantly higher DBP than low genotype group ( $n = 12$ ) at all three time points (**Figure 3**;  $F(1,28) = 5.0, p < 0.05, \eta_p^2 = 0.22$ ).

Figure 2. High vs. Low Genotype Groups: Cortisol Stress Trajectory

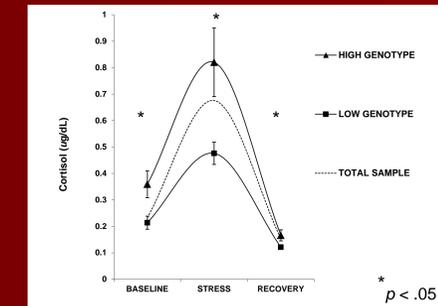
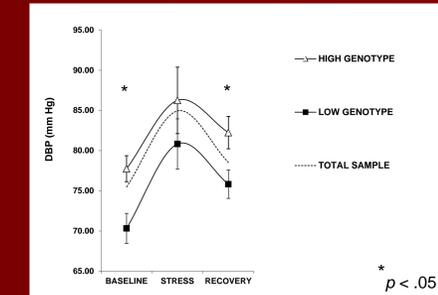


Figure 3. High vs. Low Genotype Groups: DBP Stress Trajectory



## CONCLUSIONS

- ◆ The results of this study indicate that the adrenocortical and cardiovascular stress responses in healthy male service members are influenced by both distinct and additive effects of polymorphisms in the serotonin transporter (5HTTLPR L/S), glucocorticoid receptor (Bcl1 C/G), and mineralocorticoid (-2C/G) receptor genes.
- ◆ Most notably, remarkable differences between high and low genotype groups on cortisol and DBP trajectories were observed, implying a synergistic effect.
- ◆ Pending additional study, these findings may have implications for drug discovery, gene therapy, and stress inoculation strategies.

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