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Nervous temperament in infant monkeys is associated with reduced sensitivity of leukocytes to cortisol's influence on trafficking

John P. Capitanio [a,b,*], Sally P. Mendoza [a,b], Steve W. Cole [c,d]

[a] Department of Psychology, University of California, Davis, USA
[b] California National Primate Research, University of California, Davis, USA
[c] Dept. of Medicine, Division of Hematology–Oncology, UCLA School of Medicine, Los Angeles, USA
[d] Cousins Center for Psychoneuroimmunology, University of California, Los Angeles, USA

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ABSTRACT

There is growing evidence that temperament/personality factors are associated with immune function and health-related outcomes. Neuroticism, in particular, is a risk-factor for several diseases, many with a strong inflammatory component. We propose that neuroticism (or nervous temperament in monkeys) is related to dysregulation of immune function by glucocorticoids. The present study tested the hypothesis that animals with a nervous temperament would show no relationship between cortisol concentrations and leukocyte numbers in peripheral blood (an easily obtainable measure of glucocorticoid-mediated immune function), while animals low on this factor would show expected relationships. Infant rhesus monkeys ($n = 1507$) experienced a standardized testing procedure involving blood sampling, behavioral tests, and temperament ratings. Results confirmed the hypothesis: low-nervous animals showed the expected positive relationship between cortisol levels and neutrophil numbers, while high-nervous animals showed no relationship. High-nervous animals also showed elevated cortisol concentrations at most sample points, and responded to a human challenge with more negative emotional behavior. These data suggest that individuals with a nervous temperament show evidence of glucocorticoid desensitization of immune cells. Differences with other studies, including the specific types of leukocytes that are affected, are discussed, and implications for disease processes are suggested.

1. Introduction

The idea that stable differences in behavioral dispositions are associated with health-related outcomes is an ancient one, dating back at least to Greek and Roman times, when imbalances in bodily humors were believed to be associated both with temperament and physical disease (Capitanio, 2008). While the humoral theory is no longer considered valid, empirical research has documented many links between personality or temperament traits (terms that I will use interchangeably), immune function, and health outcomes. Conceptually, the influence of such traits on health can occur via three broad, and not mutually exclusive, routes (Capitanio, in press). First, temperament can have an impact primarily through behavioral means. For example, the trait conscientiousness has long been known to be associated with longevity (Friedman, 2008), and one suggested mechanism for this relationship has been through the role of conscientiousness on health behaviors: conscientious people tend to take better care of themselves (Bogg and Roberts, 2004), which could translate into a longer lifespan. The other two ways in which temperament may influence health are more directly physiological. On the one hand, it is possible that individuals of a particular personality type are "built" differently from others, in ways that could impact a disease process. Elsewhere, we have referred to this as a "main effects" model (Capitanio, in press), and recently, we suggested an example of such a phenomenon: adult rhesus monkeys that were low in Sociability (a major personality dimension in human and non-human primates) had greater sympathetic innervation of lymph nodes compared to high-Sociable monkeys, and innervation density was negatively related to a tetanus-specific IgG response (Sloan et al., 2008). An alternative to the main effects model is an interaction model: temperament can impact health via its role in affecting coping responses – in stressful circumstances, animals with different temperament characteristics may cope in ways that lead to differences in activation of stress-response systems that can then influence immune function and disease processes (e.g., Capitanio et al., 2008).

Several studies have recently suggested that glucocorticoid (GC) regulation of inflammation may be a mechanism by which individuals may be at risk for inflammation-mediated disease. It has been long-known that one important physiologic role of GCs is to regulate immune function, and in particular, to counter inflammation

* Corresponding author at: California National Primate Research Center, University of California, One Shields Avenue, Davis, CA 95616, USA. Fax: +1 530 752 2880.
E-mail address: jpcapitanio@ucdavis.edu (J.P. Capitanio).

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(Munck and Guyre, 1986). There is growing evidence, however, that the experience of stress, particularly over long time frames, is associated with development of glucocorticoid resistance in immune cells, which can result in a reduction in the anti-inflammatory capabilities of these steroid hormones. For example, *in vitro* incubation of blood with lipopolysaccharide will stimulate inflammatory cytokine production, which will be suppressed in a dose–response fashion when different molar concentrations of GC are added to the culture. Chronically stressed individuals, however, do not show the same degree of steroid-induced suppression as do non-stressed individuals (Miller et al., 2002, 2005) – their leukocytes are more resistant to the anti-inflammatory effect of GCs. Because a principal mechanism of action of steroids is to regulate gene transcription, such results suggest that stressed individuals should show alterations in transcription of GC receptor-mediated signaling molecules. In fact, Miller et al. (2008) have reported that, compared to controls, chronically stressed humans show a down-regulation of genes that express one or more glucocorticoid response elements, and an up-regulation of genes bearing NF-κB response elements, which are components of a signaling pathway that is pro-inflammatory. Importantly, these differences were evident even in the absence of differences in cortisol concentrations. This stress-induced alteration in GC regulation of immunity may explain the seemingly paradoxical findings of stress often being associated with increased (or no change in) cortisol concentrations along with increased risk of inflammation-related disease.

While the evidence is clear that glucocorticoid resistance (GCR) can be associated with experiences such as chronic stress, it is not known whether such a mechanism might mediate temperament-related differences in disease risk, and if so, whether it is best considered a "main effect" or an "interaction effect." There is some indirect evidence that GCR may be associated with temperament, however. One of the most-studied dispositions in humans reflects a heightened tendency to show negative emotion, such as anger and hostility. The broader trait that subsumes negative affect and emotion is usually referred to as neuroticism, and has significant health consequences, having been associated with inflammation-related physical diseases such as atopic dermatitis, asthma, and irritable bowel syndrome (reviewed in Lahey (2009)). Marsland et al. (2008), studying a healthy community sample of 855 adults, found that plasma levels of the inflammatory markers IL-6 and C-reactive protein were associated with both trait negative affect and a measure of the behavioral component of hostility. While this study did not include measures of circulating cortisol concentrations, other studies have revealed higher circulating concentrations of daytime cortisol among individuals that are high in hostility and neuroticism (Nater et al., 2010; Pope and Smith, 1991; Ranjit et al., 2009; Suarez et al., 1998). Taken together, these studies illustrate the paradox referred to earlier, namely higher concentrations of cortisol associated with higher plasma concentrations of inflammatory markers, suggesting dysregulation in the HPA-immune axis. These studies further suggest that GCR might mediate the relationship between neuroticism and inflammation-related disease.

A number of measures exist that could be used to study a relationship between negative emotionality and GCR in immune cells, including cell culture and measures of transcriptional activity, as described above. Another measure is based on the fact that GCs also affect leukocyte trafficking dynamics. Administration of exogenous glucocorticoids, for example, results in increased numbers of neutrophils and decreased numbers of lymphocytes and monocytes in peripheral blood (Fauci et al., 1976). Similarly, correlations have been found in humans between cell numbers and endogenous concentrations of cortisol: positive relationships for neutrophils, and negative relationships for lymphocytes and monocytes. Importantly, socially-related stress appears to abrogate these relationships in all three cell types (Cole, 2008). We reported similar results recently from an experiment in which adult male rhesus monkeys were randomized either to non-stressful, stable social conditions, or to stressful, unstable social conditions. Animals in the stable conditions showed the expected negative relationship between cortisol concentrations and lymphocyte numbers (though no effects were found for neutrophils or monocytes), while animals in unstable social conditions showed no such relationship (Cole et al., 2009). Together, these data are consistent with the idea that chronic stress can lead to development of GCR in immune cells. While it remains to be demonstrated within a single study that leukocyte trafficking, *in vitro* cell culture as described above, and transcriptional analysis all display a consistent picture of stress-related GCR, the easy accessibility of the blood compartment makes the cortisol–leukocyte relationship an attractive and "low-tech" biomarker of this phenomenon.

The present study was undertaken to test the specific hypothesis that rhesus monkeys that show negative emotionality (which we refer to as being high in "negative temperament") would show an attenuated correlation between circulating cortisol concentrations and leukocyte numbers, compared to animals judged to be low on this temperament dimension. We had no specific predictions that nervous temperament would be related to cortisol concentrations or to leukocyte numbers; rather our interest was in the relationship between the two sets of measures. Our focus was on the three principal leukocyte subsets (neutrophils, lymphocytes, and monocytes); we also examined two lymphocyte subsets in more detail to determine whether either or both subsets might be responsible for a hypothesized effect on the broader lymphocyte class. To test our hypothesis, we make use of data obtained from a multi-year study of the causes and consequences of variation in biobehavioral organization in infant rhesus monkeys (Capitanio et al., 2006). In addition, we present additional data showing that low versus high negative temperament is also associated with measures of HPA regulation that are consistent with the idea of high-nervous animals showing GCR.

2. Methods

2.1. Subjects and living arrangements

Subjects were 1507 (639 males, 42.4%) infant rhesus monkeys (*Macaca mulatta*) born to mothers that lived in any of 17 stable, outdoor, 0.2 hectare enclosures. Each enclosure contained up to 150 animals of all ages and both sexes, which approximated the composition of a troop of rhesus monkeys in the wild. Social groups were provisioned twice daily with commercial monkey chow, twice weekly with fruits and vegetables, and water was available *ad libitum*.

2.2. Procedures

At 3–4 months of age (mean = 107.5 days, range = 89–133 days) each animal participated in a biobehavioral assessment (BBA) program conducted at CNPRC that has been described in detail elsewhere (Capitanio et al., 2005, 2006; Golub et al., 2009). Briefly, cohorts of up to eight animals at a time were separated from their mothers and relocated to an indoor testing area at 0900 h. Each animal in a cohort was housed in an individual holding cage (60 cm × 65 cm × 79 cm, Lab Products, Inc., Maywood, NJ), containing a cloth diaper, a stuffed terrycloth duck, and a novel, manipulable object. Over the next 25-h period, behavioral data were collected in a variety of standardized situations (described in Golub et al. (2009) and Capitanio et al. (2006)) and blood was