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Lines of mice with chronically elevated baseline corticosterone levels are more susceptible to a parasitic nematode infection

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Abstract

Chronically elevated circulating plasma glucocorticoid concentrations can have suppressive effects on immune function in mammals. House mice (*Mus domesticus*) that have been selectively bred for high voluntary wheel running exhibit chronically elevated (two-fold, on average) plasma corticosterone (CORT) levels and hence are an interesting model to study possible glucocorticoid-induced immune suppression. As an initial test of their immunocompetence, we compared the four replicate high runner (HR) lines with their four non-selected control (C) lines by subjecting them to infection by a parasitic nematode, *Nippostrongylus brasiliensis*. At generation 36 of the selection experiment, 10 adult males from each of the eight lines were inoculated subcutaneously with approximately 600 third-stage larval *N. brasiliensis*, and then sacrificed 12 days after injection. Neither spleen mass nor number of adult nematodes in the small intestine differed significantly between HR and C lines. However, the eight lines differed significantly in nematode counts, and the line means for nematode infestation were significantly positively related to baseline circulating CORT concentration measured in males from generations 34 and 39. Therefore, although selective breeding for high locomotor activity may not have resulted in a generally compromised immune response, results of this study are consistent with the hypothesis that glucocorticoids can have immunosuppressive effects.

Keywords: Experimental evolution; Immune response; Immune suppression; Locomotor activity; Physiological trade-off

Introduction

The Darwinian fitness of an organism hinges on appropriate allocation of resources to energetic needs, including maintenance metabolism, growth, reproduction, and immunocompetence. When internal resources are limited, increased allocation to one energetic need may come at a cost to another, thus resulting in a "trade-off" (Stearns, 1992). Interest in the physiological mechanisms that underlie trade-offs has increased in recent years, and moved beyond simple energetic considerations (e.g. Zera and Harshman, 2001; Tieleman et al., 2005; Burger et al., 2008; Garland and Rose, 2009). In particular, hormones have been viewed as good candidates for mediators of physiological trade-offs, because a single hormone often affects multiple tissues, organs or physiological processes (Stearns, 1989; Ketterson and Nolan, 1999; Sinervo and Calsbeek, 2003; Zera et al., 2007).

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As one example, glucocorticoid hormones have multiple physiological and behavioral effects (Tharp, 1975; Dallman et al., 2002; Sapolsky, 2002). In vertebrates, glucocorticoids are released throughout the day by the adrenal glands, typically in a strongly circadian pattern, and peak near the onset of the active period (at the time of lights out in nocturnal animals, e.g. Malisch et al., 2008). At basal levels, glucocorticoids are important for sustaining routine intermediary metabolism (Dallman et al., 1993, 2002; Pecoraro et al., 2005, 2006). Glucocorticoid release is elevated in response to various psychological and physical stressors, and this is crucial for rapid energy mobilization. Additionally, glucocorticoids have complex behavioral effects via the central nervous system, including effects on locomotor behavior and potentially on motivation (Lin et al., 1988, 1989; Lin and Singer, 1990; Breuner and Wingfield, 2000; Pecoraro et al., 2005, 2006).

Receptors for glucocorticoids can be found in almost all organs and tissues, including the brain, liver, muscle, spleen, and gonads (McEwen et al., 1997). Therefore, a change in circulating glucocorticoid levels has the potential to alter multiple aspects of behavior and physiology, including locomotion, metabolism, and immune function. Increased plasma corticosterone (CORT, the main glucocorticoid in rodents) increases energy availability by promoting proteolysis, lipolysis, and gluconeogenesis (Tharp, 1975; Dallman et al., 1993, 2002). Because most stressors are associated with increased energetic needs, it is generally presumed that increased release of CORT in response to stress is adaptive and has evolved to help meet these energetic needs while simultaneously curtailing processes that are not immediately necessary, such as immune function, growth, and reproduction (Sapolsky et al., 2000; Sapolsky, 2002). Although increasing the concentration of circulating CORT would seem to be of obvious survival value as a response to acute, short-term stressors, chronically elevated CORT levels have been associated with immune, reproductive, and growth suppression in birds and mammals (Wingfield et al., 1998; Sapolsky, 2002; Romero et al., 2005; Johnson et al., 2006).

Here, we report an initial investigation of immune function in mice selectively bred for high levels of voluntary locomotor activity. As compared with four non-selected control (C) lines, the four replicate high runner (HR) lines exhibit an increase of almost 200% in daily running distance, and a similar increase in home-cage activity when deprived of wheels (Swallow et al., 1998, 1999; Garland, 2003; Rhodes et al., 2005; Malisch et al., 2008). Several types of behavioral and neurobiological evidence indicate that the motivation and/or reward systems of the brains of HR mice have been altered (Bronikowski et al., 2004; Rhodes et al., 2005; Belke and Garland, 2007). In addition, a number of traits have evolved in a way that seem to represent adaptations to permit high levels of sustained, aerobically supported exercise, including elevated maximal oxygen consumption, increased hindlimb symmetry, and larger femoral heads (Garland, 2003; Garland and Freeman, 2005; Rezende et al., 2006; Middleton et al., 2008; references therein).

Mice from the HR lines also exhibit a two-fold increase in baseline plasma CORT levels (Malisch et al., 2007). The increased plasma CORT level has been interpreted as an adaptation to promote or support high locomotor activity (e.g. see Malisch et al., 2007, 2008). However, the elevated CORT levels are associated with reduced growth rates and lower body size in the HR lines (Girard and Garland, 2002; Malisch et al., 2007), which may represent a cost.

The goal of the present study was to test the hypothesis that the elevated CORT levels in the HR lines are associated with a cost in terms of immune function. Among other effects on immune function, elevated glucocorticoids may interfere with clearance of a parasitic infection by inhibiting cytokine release, reducing cytokine receptor levels, blocking maturation of T lymphocytes, and increasing lysis of T lymphocytes (McEwen et al., 1997; Sapolsky et al., 2000). Therefore, we hypothesized that HR lines would have a reduced ability to clear a parasitic infection. In addition, the replicate HR and control lines show significant differences in circulating CORT levels, wheel running, body mass, and other traits (e.g. Swallow et al., 1998, 1999; Rezende et al., 2006; Malisch et al., 2007), so we also tested for a positive relation between line means of circulating CORT levels (obtained from Malisch et al., 2007; Malisch et al., 2008) and the number of nematodes remaining in the small intestine 12 days after inoculation (see below).

Materials and methods

Study animals

The replicated selective breeding experiment began from a base population of outbred Hsd:ICR mice. The selection criterion was total revolutions run on days 5+6 of a 6-day exposure to a Wahman-type activity wheel (1.12 m circumference) when mice were ~7–9 weeks of age (Swallow et al., 1998; Garland, 2003; Rhodes et al., 2005). For the present study, 10 adult males from each of the four replicate HR lines and four non-selected C lines were studied, sampled from generation 36. As in the routine selection protocol (Swallow et al., 1998), all animals used in this experiment were weaned at 21 days of age, toe-clipped for identification, and housed in same-sex groups of