Immune and Hormonal Changes following Intense Military Training

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This study was designed to determine whether the immune and hormonal systems were affected by a 5-day military course following 3 weeks of combat training in a population of 26 male soldiers (mean age, 21 ± 2 years). The combination of continuous heavy physical activity and sleep deprivation led to energy deficiency. At the beginning of the training program and immediately after the combat course, saliva samples were assayed for secretory immunoglobulin A and plasma samples were assayed for interleukin-6, dehydroepiandrosterone sulfate, prolactin, catecholamines, glucocorticoids, and testosterone. Secretory immunoglobulin A was lower and circulating interleukin-6 was increased by the end of the course, which was attributed to sympathoadrenergic stimulation. Dehydroepiandrosterone sulfate, prolactin, and testosterone levels fell significantly. These results suggest that prolonged and repeated exercise such as that encountered in a military training program induces immune impairment via a decrease in mucosal immunity and a release of interleukin-6 into the circulation. The impaired secretion of dehydroepiandrosterone sulfate and prolactin, two immunomodulatory hormones, was thought to be a response to the chronic stressors. Lowered testosterone reflects a general decrease in steroid synthesis as a consequence of the physical and psychological strain.

Introduction

The body is often exposed to combinations of stressors, especially in military operations where the stressors are often prolonged, hard, continuous physical exercise combined with sleep, energy, and water deficiency, cold, heat, time pressure, or periods of waiting and inactivity.[1-3] The effects of these various stressors on the soldier's health are complex but could be deleterious, as it has been shown that chronic stress experienced by soldiers in wartime leads to immunosuppression.[4]

Recently, Brenner[5] reported that 18 weeks of basic infantry training did not have an adverse impact on either immune function or the incidence of upper respiratory tract infections (URTIs). In contrast, Kramer et al.[6] in a study of the effects of food restriction during a military training on T lymphocyte proliferative responses in vitro found that (i) the military training program reduced the T lymphocyte proliferative response and (ii) that this was enhanced if the soldiers had a restricted diet. Impaired cellular immune responses have also been evidenced in soldiers after 8 weeks of stressful training.[7]

In athletes, epidemiological studies have noted an increase in infections, especially URTIs, after severe physical stress such as marathon[8] or ultramarathon runs.[9] Resistance to respiratory infections is provided by the mucosal system with the major immunoglobulin being secretory immunoglobulin A (IgA). A decrease in salivary IgA concentration has been proposed as a marker of excessive training, which could help to identify athletes more prone to or at risk from respiratory illness.[10]

Previous studies on mucosal immunity have focused on the acute changes in IgA levels after individual sessions of intense exercise or training. They have described consistent decreases or a chronic suppression of salivary IgA along with an increased incidence of respiratory illness.[10-12]

On the other hand, muscle cell injury and high, sustained metabolic work rates caused by prolonged exercise (e.g., marathon) have been demonstrated to involve a sequential release of proinflammatory cytokines and more particularly interleukin (IL)-6.[13] The proinflammatory cytokines help regulate the inflammatory cascade and are considered to be primary mediators for repair processes in muscle cells and metabolically active tissues.[14]

The present study was designed to find out whether a military training in the French Army comprising 3 weeks of conditioning followed by a 5-day combat course induced specific alterations in the immune and hormonal systems. The 5-day course included heavy and continuous physical activities inducing energy deficiency associated with psychological strain and sleep deprivation. In a study of hormonal adaptation, we recently evidenced lowered leptin levels, an index of energy availability, after this training schedule.[3] Other metabolic and hormonal changes during the combat course have been documented by our laboratory.[2]

The immune mucosal system was studied by determination of salivary IgA concentrations and IgA relative to total protein before the training and immediately after the 5-day course. In addition, the immune system was studied by assay of circulating IL-6. In view of the putative immunomodulatory action of dehydroepiandrosterone sulfate (DHEAs) and prolactin during chronic stress,[15] we measured plasma DHEAs and prolactin during the military training program. In an attempt to discern mechanisms responsible for alteration in immune status, we also assayed circulating glucocorticoids and catecholamines. We also focused on the consequences of psychological and physical restraints on steroid synthesis via changes in plasma testosterone levels.

Methods

Subjects

A group of 26 male cadets (mean age, 21 ± 2 years) from the French Military Officer School took part in a 4-week military

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endurance training program. The subjects were in good mental and physical condition. After 3 weeks of physical training, they then participated in a 5-day combat course. A French medical ethics committee (Faculty of Medicine Paris V, France) approved the study, and the participants gave their voluntary written consent.

Training Program and Combat Course

Anthropometric measurements were made at entry into training and at the end of the combat course. The training and the 5-day combat course took place at the National Center for commando training at Mont-Louis in the Pyrenees mountains, over 96 hours from 6:00 p.m. on day 1 until 6:00 a.m. on day 5. The course took place in June with temperatures ranging between 18°C and 25°C. The subjects walked distances of 25 to 35 km at night across the countryside avoiding roads, lanes, and trails. They carried backpacks of 11.0 ± 1.2 kg.

During the 5-day course, the total uphill and downhill walking distance was 2,800 m. Several parts of the course involved mountain climbing. In addition to walking, the subjects took part in frequent simulated combat activities. The continuous activity allowed only a few periods of sleep, amounting to 3 to 4 hours every 24 hours.

Diet

During the course, the subjects ate the commando ration with a mean daily energy content of 3,200 kcal. This ration of a mean mass of 900 g consisted of two freeze-dried meals (Lyofal, France) of 480 kcal each, 1,200 kcal of bread in the form of biscuit, and 1,000 kcal of energy bars, chocolate, and candied fruit. The percentage of each class of nutrient in the total energy supplied was 55% carbohydrate, 30% lipid, and 15% protein.

Levels of Energy Expenditure

The combat course resembles the conditions studied by Opstad[1] and the previous studies of our laboratory.[2,3] Based on these studies, we considered that the subjects had physical exercise activities corresponding to 35% of maximal oxygen uptake and a daily energy expenditure during the course exceeding 5,000 kcal.

Blood Sampling

Blood sampling took place before the 3 weeks of the training program (i.e., the subjects being still in their Officer School) and at the end of the 5-day course. The first set of samples was taken between 7:00 a.m. and 8:00 a.m. Before the sampling, the subjects were requested to eat a light breakfast to simulate the conditions of the second sampling. The second sampling, at the end of the course, took place between 5:00 a.m. and 6:00 a.m. For the second sampling, the subjects were conducted to a military barracks for medical and scientific investigations. All subjects were weighed on the sampling days.

Twenty milliliters of venous blood were sampled from an antecubital vein after a 10-minute rest supine. After clotting at 4°C, the plasma was stored at −80°C for subsequent determinations in our laboratory.

Saliva Collection

Saliva samples were taken after blood sampling before the 3 weeks of the training program and at the end of the 5-day course. The saliva samples were obtained using a standardized procedure.[11] The subjects sat in an upright position with the head inclined forward. The subjects rinsed their mouth with sterile water and were then asked to collect saliva in the mouth for 1 minute, after which they were asked not to swallow during 5 minutes. The subjects were told not to force salivation, and it was not (artificially) stimulated. Immediately after the 5-minute period, the saliva sample was placed on ice then stored at −80°C until subsequent determinations in our laboratory.

Salivary IgA and Protein Determination

Salivary IgA concentrations were determined by a modified nephelometric method (IGALC, IgA low concentration, Immunochemistry IMMAGE system, Beckman Coulter, Roissy, France) generally used for assay of human IgA in serum and cerebrospinal fluid (CSF). Saliva samples were centrifuged before analysis. Saliva was diluted 1:72 (expected values <120 mg·L^{-1}) or 1:432 (expected values >120 mg·L^{-1}), and the limits of sensitivity were 18 mg·L^{-1} for serum and 0.25 mg·L^{-1} for CSF.

Protein concentrations were determined using a colorimetric method for clinical use in CSF and urine (urinary/CSF protein, AU600 Application, Olympus System Reagent, Olympus France, Rungis, France). Maximal linearity is 2,000 mg·L^{-1}.

Plasma IL-6 Assay

Plasma IL-6 concentrations were determined using quantitative high-sensitive sandwich enzyme-linked immunosorbent assay kits provided by R&D Systems (Minneapolis, Minnesota). All samples and standards were analyzed in duplicate. The plasma IL-6 concentrations were determined from the standard curve by linear regression. The minimum detectable concentration was <0.094 pg·mL^{-1}.

Plasma Hormones

Prolactin, DHEAs, testosterone, adrenocorticotropic hormone (ACTH), and cortisol concentrations were assayed in duplicate by radioimmunoassay using commercial kits (DiaSorin, Antony, France). The adult normal ranges were: 2.6 to 7.2 ng·mL^{-1} for prolactin; 1,330 to 4,410 ng·mL^{-1} for DHEAs; 10 to 30 nmol·L^{-1} for testosterone; 0 to 71 pg·mL^{-1} for ACTH; and 193 to 690 nmol·L^{-1} for morning cortisol. The limits of sensitivity were: 0.5 ng·mL^{-1} for prolactin; 60ng · mL^{-1} for DHEAs; 0.18 nmol · L^{-1} for testosterone; 15 pg·mL^{-1} for ACTH; and 5.79 nmol·L^{-1} for cortisol.

Epinephrine, norepinephrine, and dopamine were assayed by high-performance liquid chromatography with electrochemical detection adapted from the method described by Smedes et al.[16]

Statistics

Results are expressed as the mean ± SEM of absolute valuės. Paired Student's t test following one-way analysis of variance was used to identify differences. Pearson's test was used for the correlation analysis. $p < 0.05$ was considered to indicate significance.

Results

Body Mass Index

At the beginning of the training program, the mean of the body mass index was 24.07 ± 0.38 kg/m^2 and 23.74 ± 0.39 kg/m^2 at the end. The difference was not significant.

Salivary IgA and Protein Concentrations-IgA Relative to Protein

The mean IgA concentrations fell from 91.8 ± 7.4 mg·L^{-1} before the training program to 68.4 ± 8.7 mg·L^{-1} after the 5-day course ($p < 0.05$). The mean protein concentration was 890 ± 70 mg·L^{-1} before the training program and 760 ± 60 mg·L^{-1} after the 5-day course (not significant). The mean IgA/protein ratio decreased from 13.0 ± 2.0% to 8.0 ± 1.0% ($p < 0.05$; Fig. 1).

Plasma IL-6 Concentration

The mean IL-6 concentration increased from 2.84 ± 0.11 pg·mL^{-1} before the training program to 3.95 ± 0.55 pg·mL^{-1} after the 5-day course ($p < 0.05$; Fig. 2).

Plasma DHEAs and Prolactin Concentrations

The mean DHEAs decreased from 4,060 ± 629 ng·mL^{-1} to 2,347 ± 246 ng·mL^{-1} ($p < 0.01$). The mean prolactin decreased from 6.86 ± 0.43 ng·mL^{-1} to 4.19 ± 0.29 ng·mL^{-1} ($p < 0.001$; Fig. 3).

Plasma Cortisol, Catecholamines, and Testosterone Concentrations

The mean testosterone decreased from 15.1 ± 0.7 ng·mL^{-1} to 9.8 ± 0.6 ng·mL^{-1} ($p < 0.001$). Mean cortisol, ACTH, and epinephrine were not altered by the training program, although norepinephrine was significantly increased (296 ± 17 ng·L^{-1} vs. 672 ± 48 ng·L^{-1}; $p < 0.001$). Mean dopamine was significantly increased (23 ± 3 ng·$^{-1}$ vs. 40 ± 5 ng·L^{-1}; $p < 0.01$). Results are shown in Table I.

Correlations between Parameters

A significant correlation was noted between plasma IL-6 and norepinephrine concentrations after the course ($r = 0.4831$; $p < 0.05$). No correlations between the other variables were detected either before or after the training course.

Discussion

This study provides evidence that a long-lasting exertion, such as a military training, induces alterations in the immune system by (i) suppression of mucosal humoral immunity, reflected by a reduction in salivary IgA and IgA/protein ratio, and (ii) release of plasma IL-6, a proinflammatory cytokine. The combat training program is of particular interest as the uniform and predictable nature of the stressors and the homogeneit, and good health of the soldiers provide a unique opportunity for investigating the hormonal and immunological effects of chronic stress that leads to a state of energy deficiency.[1,2] Interestingly, this training schedule has been shown to decrease levels of leptin,[3] a hormone secreted by adipose tissue, which is regarded as an index of energy availability. Leptin levels are reduced by physical and psychological stressors as a consequence of energy deficiency, and a lowered leptin is associated with impaired immune responses.[17]

There are few data on the consequences of repeated and prolonged exposure to multifactorial stressful conditions on the immune system. However, it is known that dysregulation of immune and hormonal systems is one of the features of the Overtraining Syndrome,[18] which arises when body homeostasis is threatened. Soldiers may also be overtrained.[19]

As in exercise studies, conflicting results have been reported

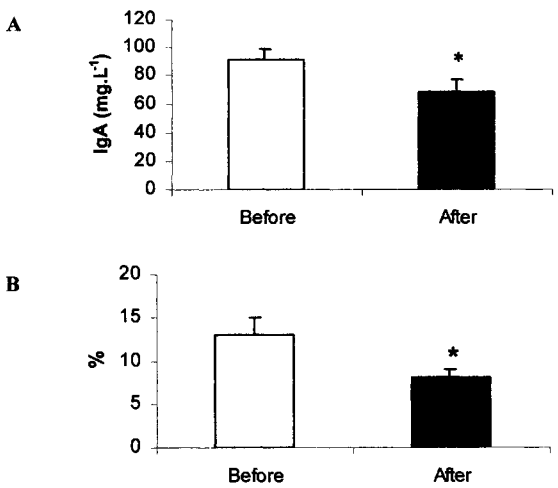

Fig. 1. Saliva concentration of IgA (milligrams per liter) (A) and relative amount of IgA to protein (percent) (B) before the training program (□) and after the 5-day combat course (■) (mean ± SE). *, Results differ before and after the combat course ($p < 0.05$, $N = 26$).

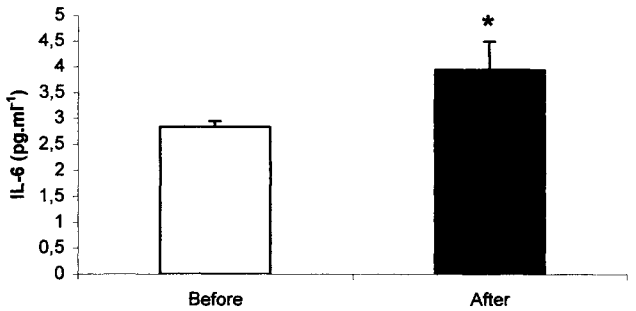

Fig. 2. Plasma concentration of IL-6 (picograms per milliliter) before the training program (□) and after the 5-day combat course (■) (mean ± SE). *, Results differ before and after the combat course ($p < 0.05$, $N = 26$).

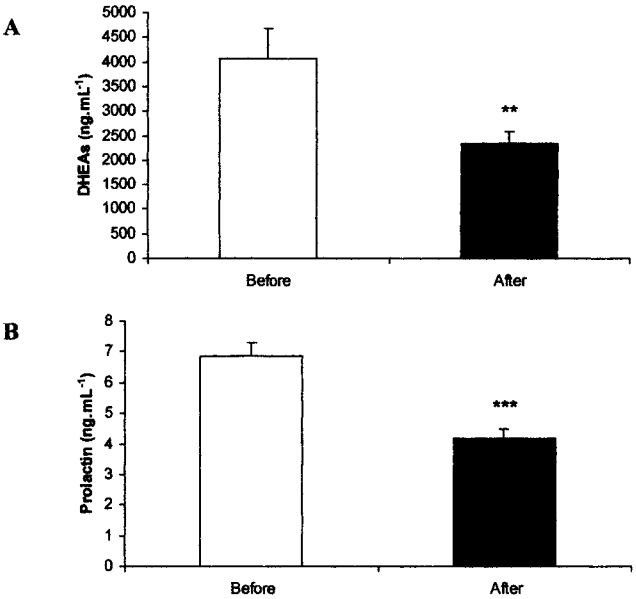

Fig. 3. Plasma concentrations of DHEAs (nanograms per milliliter) (A) and prolactin (nanograms per milliliter) (B) before the training program (□) and after the 5-day combat course (■) (mean ± SE). ** and ***, Results differ before and after the combat course ($p < 0.01$ and $p < 0.001$, respectively, $N = 26$).

TABLE I

BLOOD HORMONE CONCENTRATIONS MEASURED BEFORE THE TRAINING PROGRAM AND AFTER THE 5-DAY COURSE

	Cortical (nmol/L)	ACTH (pg/mL)	Norepinephrine (ng/L)	Dopamine (ng/L)	Epinephrine (ng/L)	Testosterone (nmol/L)
Before	440 ± 20	34.5 ± 2.0	296 ± 17	23 ± 3	29 ± 3	15.1 ± 0.7
After	452 ± 21	34.6 ± 2.8	672 ± 48[a]	40 ± 5[b]	36 ± 5	9.8 ± 0.6[a]

[a] Indicate that results differ before and after the training ($p < 0.001$, $n = 26$).

[b] Indicate that results differ before and after the training ($p < 0.01$, $n = 26$).

on the influence of military training on the immune system. A basic infantry training does not appear to affect immune function or the incidence of URTIs,[5] but impaired cellular immune responses have been evidenced after 8 weeks of stressful military training.[7] The energy deficiency during military training appears to be the main factor altering in vitro lymphocyte proliferative responses.[6]

In our study, the observed increase in plasma IL-6 is in agreement with most of the findings on exercise-related alterations in cytokine levels.[13] The moderate but significant increase in IL-6 represents an inflammatory phenomena consistent with the type of training, which was prolonged but of moderate intensity (approximately 35% $Vo_{2\ max}$).[2] The increase in plasma IL-6 levels is thought to be the consequence of an activation of the sympathetic nervous system by prolonged exercise.[20] Consistent with this idea, we noted a significant elevation in plasma norepinephrine at the end of the course. Indeed, the spleen produces as much as 50% of the total circulating IL-6, and the thymus and other immune organs are heavily innervated by the sympathetic system. The sympathetic nervous activation would therefore be expected to stimulate IL-6 production and/or secretion.[20]

Studies on the effects of training on the mucosal immune system evidence decreased salivary IgA levels and increased susceptibility to respiratory illness.[10,12] In addition, a recent study showing differences in salivary IgA concentration and/or secretion in response to mental, cold, and exercise stress suggested that the various stressors in the military training might act in different ways on the secretory IgA response.[21] Our results show that the absolute concentration of IgA and the IgA relative to total protein were reduced after both the combat course and the 3-week physical training. The mechanisms responsible for the exercise-induced fall in IgA remain to be elucidated. Secretory IgA are secreted by plasma cells beneath the ascinar epithelium in salivary glands, and transport of IgA across the epithelial barrier requires a secretory component.[22] Furthermore, the sympathetic nervous system is a likely candidate for the rapid modulation of salivary IgA. For example, the rapid reduction in IgA after a short-term cold stress has been shown to be mediated by α-adrenergic systems.[21] In our study, we noted a reduction in secretory IgA suggesting (i) that at least one of the processes involved in IgA transport and secretion may have been affected by the training or (ii) a possible influence of the sympathetic nervous system.

Our study indicated an immunosuppressive effect of the military training program on the mucosal system along with release into the circulation of the proinflammatory cytokine IL-6, one of the most potent mediators of the acute phase response. We had circumstantial evidence that the immunosuppressive and inflammatory effects of the training may have stemmed from hormonal actions. For instance, the training induced norepinephrine release as a consequence of a stimulation of the sympathetic nerve terminals. As previously shown,[23] the hormonal responses of the adrenal gland seems to adapt to the intensity of physical stress as epinephrine and cortisol levels were unchanged at the end of the course.

Our study showed that the military training reduced levels of two immunomodulatory hormones, DHEAs and prolactin, which was attributed to its stressful nature. Additionally, we showed a general lowering effect on steroid synthesis indicated by reduced testosterone. Lowered DHEAs is typically related to the Chronic Fatigue Syndrome.[24] Although we did not evidence a direct link between the lower levels of DHEAs and the immunosuppression, it is of interest in view of the putative role of DHEA in modulating immune responses. This natural hormone has been shown to protect mice from lethal viral and bacterial infections.[25] Furthermore, levels of DHEAs decline with age in humans, and a dysregulation of the immune system is often found in such populations (e.g., raised IL-6 serum levels in the elderly associated with chronic conditions such as arthritis).[26] The link between low levels of DHEAs and increased IL-6 in blood may be accounted for by the finding that DHEA enhances the activity of the Th1 subtype of CD4 cells and consequently the balance between Th1 and Th2 CD4 cells.[27] Thus, lowered DHEAs levels may upset the balance between Th1 and Th2 CD4 cells in favor of Th2 CD4 cells, which secrete IL-6.

Prolactin has been shown to possess multiple homeostatic roles in the organism. This peptide hormone seems to act as an immunostimulatory mediator during the response to environmental and physiological stress.[15] We observed here a marked decrease in prolactin probably under the inhibitory influence of a training-induced elevation in dopamine, the main inhibitory neurotransmitter and neurohormone for prolactin secretion.[28] Lowered prolactin levels have been described after a similar combat course[1] and are considered as a chronic stress-related phenomenon, which could induce immunosuppression.[15]

In conclusion, the present study demonstrated a suppression of the mucosal immune system (i.e., lowered salivary IgA levels), associated with a release of the proinflammatory cytokine, IL-6, into the circulation at the end of a 5-day combat course following 3 weeks of military training. The sympathoadrenergic activation induced by repeated and prolonged exercise during the combat course may account for the observed immune responses. Circulating levels of DHEAs and prolactin, two immunostimulatory hormones, were also reduced by the long-term physical stress combined with energy and sleep deprivation. Studies are being designed by our laboratory to correlate the observed immune changes to clinical findings on URTIs.

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