Effects of age and recombinant equine somatotropin (eST) administration on immune function in female horses

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ABSTRACT: Aging has been associated with declines in somatotropin and IGF-I levels as well as declines in immune function. To determine the effects of age and whether ST administration could reverse immunosenescence in horses, eight young and eight aged female standardbred horses were given 10 mg/d recombinant equine somatotropin (eST) or vehicle buffer for 49 d. Plasma IGF-I concentrations in both age groups were higher in eST-treated animals (P < 0.001), and higher in young eST-treated mares than in aged eST-treated mares during wk 4 to 7 (P < 0.001). There was a trend toward lower monocyte and granulocyte numbers (P = 0.07) in mares treated with eST. Aged mares treated with eST had lower lymphocyte numbers (P < 0.005). The percentage of CD4+ lymphocytes was higher in aged mares (P < 0.001), and the percentage of CD8+ lymphocytes was higher in young mares (P < 0.01). Lymphocyte proliferation in response to concanavalin A, phytohemagglutinin, and pokeweed mitogen was not lower in aged mares (P = 0.17, 0.17, and 0.13 respectively). Aged mares treated with eST showed a lower peak primary antibody response to keyhole limpet hemocyanin (P < 0.05). Young mares treated with eST showed a higher peak primary antibody response to keyhole limpet hemocyanin (P < 0.05). Like other species, horses exhibit similar signs of age-related declines in various immune parameters, but those of aging were not reversed with eST treatment.

Key Words: Aging, Horses, Insulin-like Growth Factor, Senescence, Somatotropin

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Introduction

Investigations of the interrelationship between the aging process and immune dysregulation in aged humans and mouse models (reviewed by Miller, 1995) have examined the number and functions of cells and the factors that influence cellular and humoral innate and acquired immunity. Researchers have reported age-related decreases in monocyte activity (Antonacci et al., 1984) and neutrophil function (Ginaldi et al., 1999) in aged populations of rodents and humans. Several studies examining T cell number and function have been reviewed by Saltzman and Peterson (1987). Results of research examining the effects of aging and exercise stress on immune function in standardbred mares (Horohov et al., 1999) suggest that older horses experience age-related immune function phenomena similar to those that have been observed in other species. Lymphocyte proliferative ability as well as cytokine stimulation and production decrease with age in horses (Horohov et al., 1999). Reductions in antibody response to specific antigens with increasing age have been reported (reviewed by Saltzman and Peterson, 1987), and older horses have demonstrated lower antibody titers to equine influenza virus compared with younger horses (Horohov et al., 1999).

Researchers examining neuroendocrine-immune interactions have characterized immunoregulatory properties of various hormones, including somatotropin. Somatotropin administration enhanced immune cell function in heifers and humans (Elvinger et al., 1991; Kelley, 1990). Somatotropin stimulated immune cell function in aged monkeys (LetRoith et al., 1996). Malinowski et al. (1997) reported that recombinant equine somatotropin had a positive impact on age-related declines in body condition, muscle tone, and nutrient utilization in horses. The present study was designed to quantify the effects of aging on the immune system and...
to examine the immunomodulatory effects of somatotropin administration.

**Materials and Methods**

**Animal Care and Management**

Eight aged (mean = 25.0 yr ± 0.8) and eight young (mean = 5.9 yr ± 0.7) female standardbred horses were housed in box stalls at night and on drylot during the day at the Equine Research Facility, New Jersey Agricultural Experiment Station, New Brunswick, New Jersey. Mean BW values were obtained before the beginning of the trial (Table 1). Horses were fed a diet of commercialized pellet (Brown’s and Sons, Inc., Birdsboro, PA) and alfalfa cubes (Semican, Pessisville, Quebec, Canada; for diet composition, see Table 2) to maintain BW; aged horses at 125% National Research Council (NRC, 1989) recommendations and younger horses at 110% NRC (Ralston, 1990). Weigh-backs were performed daily. Horses were given ad libitum access to salt and water. In order to remove the potential effects of estrous related events on immune function, estrous cycle was regulated via a pretrial i.m. injection of 10 mg in 2 mL of prostaglandin F$_2$α (PGF$_2$α) (Lutalyse, Pharmacia and Upjohn Company, Kalamazoo, MI) and daily oral progesterone given at 0.44 mg/kg (Regumate, Hoechst Roussel, Somerville, NJ) throughout the experiment.

Horses were separated into four groups, with half of the aged mares given equine somatotropin (eST) (n = 4) and the others given controls (n = 4), and half of the young mares given eST (n = 4) and the others given controls (n = 4). Blood sampling, Regumate administration, and eST injections were conducted preceding the morning feeding. Treated mares were given i.m. 10 mg/d eST in 2 mL of glycine mannitol buffer (EquiGen, Bresagen, Ltd.; Adelaide, SA, Australia) daily for 49 d. Control mares were given 2 mL of buffer. On d 28 of eST treatment, 1 mg of keyhole limpet hemocyanin (KLH) (Calbiochem-Novabiochem Corporation, La Jolla, CA) in 1 mL of sterile sodium chloride (0.9%) was administered i.m. to determine primary antibody response. The dose of KLH was chosen based on a previous study that demonstrated that 1 mg was efficacious in eliciting an appropriate primary antibody response (D. W. Horohov, personal communication). The KLH antibody response was determined in serum collected on d 0, 3, 7, 10, 17, 24, and 38 after KLH treatment.

Weekly plasma IGF-I was determined by RIA (Christensen et al., 1997). The intraassay coefficients of variation for young pool and aged pool were 5.4 and 5.9% respectively.

Weekly serum progesterone concentrations were determined by RIA (Malinowski, et al., 1985). The intra and interassay coefficients of variation were 14.2 and 8.7% respectively.

**Immunological Assays**

Heparinized blood samples for immunological assays were collected on d 0, 28, and 49 of eST treatment. Peripheral blood lymphocytes, granulocytes, and monocytes were quantified using a flow cytometer (Coulter Epics/Profile II, Beckman-Coulter Inc., Miami, FL) on d 0, 28, and 49 of eST treatment. To quantify T cell subsets, anti-equine CD4$^+$ and anti-equine CD8$^+$ monoclonal antibodies (cell line HB61A and HT14A, Isotype

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**Table 1. Effects of age and 49 d of recombinant equine somatotropin administration on feed offered, feed refused, and body weight**

<table>
<thead>
<tr>
<th></th>
<th>Feed offered</th>
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<th>Feed refused</th>
<th></th>
<th>Mean body weight</th>
<th></th>
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<tr>
<td></td>
<td>d 1</td>
<td>d 49</td>
<td>d 1</td>
<td>d 49</td>
<td></td>
<td>d 1</td>
</tr>
<tr>
<td>Young (control)</td>
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<td>9.1</td>
<td>0.2</td>
<td>0.2</td>
<td>557.1</td>
<td>551.8</td>
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<tr>
<td>SEM</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td>20.6</td>
<td>20.6</td>
</tr>
<tr>
<td>Young (eST)</td>
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<td>8.1</td>
<td>0.2</td>
<td>0.2</td>
<td>533.6</td>
<td>543.8</td>
</tr>
<tr>
<td>SEM</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td>20.6</td>
<td>20.6</td>
</tr>
<tr>
<td>Aged (control)</td>
<td>8.7</td>
<td>8.6</td>
<td>0.2</td>
<td>1.0</td>
<td>473.9</td>
<td>483.8</td>
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<td>SEM</td>
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<td>0.2</td>
<td>0.2</td>
<td>20.6</td>
<td>20.6</td>
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<tr>
<td>Aged (eST)</td>
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<td>0.2</td>
<td>506.3</td>
<td>522.0</td>
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<tr>
<td>SEM</td>
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<td>0.2</td>
<td>0.2</td>
<td>20.6</td>
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</tr>
</tbody>
</table>

aData are displayed as means (kilograms) ± SEM.

x,yDifferent superscripts denote differences between treatment groups at a particular time point ($P < 0.05$).

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**Table 2. Composition of diet (DM basis)**

<table>
<thead>
<tr>
<th></th>
<th>DM</th>
<th>CP</th>
<th>ADF</th>
<th>NDF</th>
<th>Crude fat</th>
<th>NSC</th>
<th>Ca</th>
<th>P</th>
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<td>39.1</td>
<td>51.6</td>
<td>—</td>
<td>19.5</td>
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<td>0.2</td>
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<tr>
<td>Concentrated pellet</td>
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<td>17.1</td>
<td>17.7</td>
<td>32.5</td>
<td>—</td>
<td>—</td>
<td>1.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

aData as analyzed by DHI Forage Testing Laboratory, Ithaca, NY.
IgG1, VMRD, Inc., Pullman, WA) were purified on a protein FPLC brand (Amersham Pharmacia Biotech, Piscataway, NJ) low-pressure liquid chromatograph using affinity chromatography (HiTrap Protein G; AP Biotech, Piscataway, NJ). Purified concentrated antibodies were conjugated to fluorescent label (Quick Tag FITC Conjugation Kit; Boehringer Mannheim Corp., Indianapolis, IN) and bound to equine CD4+ and CD8+ lymphocytes for quantification via flow cytometry.

To determine lymphocyte proliferative ability, equine peripheral blood mononuclear cells were isolated by differential centrifugation over Histopaque (Sigma, St. Louis, MO), washed with calcium and magnesium-free PBS, and suspended at a concentration of 2 × 10^6 cells/mL in RPMI 1640 supplemented with 25 mM HEPES buffer, 2 mM L-glutamine, 2 g/mL NaHCO3, 5.5 × 10^−6 M 2-mercaptoethanol, 100 U/mL penicillin, 100 µg/mL streptomycin, and 5% heat-inactivated fetal bovine serum. Cells were transferred to 96-well, round-bottomed microtiter plates (Corning Glass Works, Corning, NY) at a concentration of 2 × 10^5 cells/well and cultured with 4 µg/mL of mitogens (Sigma, St. Louis, MO), including: concanavalin A (ConA), phytohemagglutinin (PHA), and pokeweed mitogen (PWM) or media alone. After incubation for 3 d at 37°C and 5% CO2, cells were pulsed with 5 µCi of [3H]thymidine per well for 4 h. Cultures were then harvested using a cell harvester onto glass fiber filter paper and counted in a liquid scintillation counter. Results were calculated as net counts per minute by subtracting the [3H]thymidine incorporation (in counts per minute) of the PBMC cultures containing medium alone from the [3H]thymidine incorporation (in counts per minute) of the cultures stimulated with mitogen (Horohov et al., 1999).

Serum antibodies to KLH were determined by ELISA. Immulon flat-bottomed microtitre plate (Dynex Technologies, Chantilly, VA.) wells were coated with 250 ng of KLH (CalBiochem-Novabiochem Corp., La Jolla, CA.) in 50 µL of ELISA coating buffer (0.015 M Na2CO3, 0.035 M NaHCO3, 0.003 M NaN3) in each well for 16 h at 4°C. Plates were washed three times with a solution of 0.05% Tween 20 in PBS (PBST) and then nonspecific binding sites were blocked using 300 µL/well of 1% fish gelatin in PBS (PBSG) for 1 h at room temperature. Plates were washed three times with PBST. Serum from one horse at one time point (d 17) was diluted with PBSG for positive (1:10) and negative (1:6,400) controls. All serum samples were diluted with PBSG 1:200, the optimal dilution determined for analysis. Fifty microliters of each diluted sample was aliquoted per well in triplicate. Plates were incubated for 90 min at 37°C and then washed three times with PBST, blocked, and washed. Affinity-purified, horseradish peroxidase-conjugated goat anti-equine IgG, heavy- and light-chain specific (Jackson Immunoresearch Labs, West Grove, PA), was diluted 1:40,000 in PBSG and added to each well in 50-µL aliquots. Plates were incubated for 60 min at 37°C and then washed three times with PBST, blocked, and washed. Seventy-five microliters of prewarmed 3,3′,5,5′-tetramethylbenzidine (Kirkegaard and Perry, Gaithersburg, MD) substrate was added to each well. Reactions were allowed to proceed for 10 min for optimum color development and stopped with STOP solution (Kirkegaard and Perry, Gaithersburg, MD). Optical density (OD) was recorded at 450 nm using an automated ELISA reader (Biorad Laboratories, Hercules, CA).

**Statistical Analysis**

Data were analyzed by analysis of variance for repeated measures using the general linear models procedure of SAS (SAS Institute Inc., Cary, NC). The model included treatment, time and age as main effects; and the interactions: treatment × time, treatment × age, time × age, and treatment × time × age (Malinowski et al., 1997). When main effects differed significantly (P < 0.05), the means were compared by least significant difference tests with rejection of the null hypothesis when P < 0.05. Least squares means ± SEM are reported throughout.

**Results**

Daily feed intake, feed refused, and BW values were not affected by eST treatment (Table 1).

Weekly serum progesterone levels indicated that 5 of the 16 mares began cycling and actually ovulated (progesterone > 1 ng/mL) during the last 2 wk of the experiment. Two of the 16 mares displayed prolonged luteal function indicated by progesterone concentrations > 1 ng/mL throughout the experiment.

Weekly IGF-I levels (Figure 1) were significantly higher in eST-treated than in control mares (P < 0.001). There was an age × treatment interaction (P < 0.05) because IGF-I concentrations were higher in aged eST-treated mares than in young eST-treated mares on wk 5 and 6.

Monocyte and granulocyte counts tended to be lower (P = 0.07) in mares treated with eST. Aged mares treated with eST displayed lower lymphocyte numbers when compared with other treatment groups (P < 0.05).

With regards to T cell subsets (Figure 2), a higher percentage of blood lymphocytes were CD4+ (P < 0.001) in aged mares, but a higher percentage of blood lymphocytes were CD8+ in young mares (P < 0.01). The CD4:CD8 ratio was higher in aged mares than in young mares (4.0 and 2.9 ± 0.2 respectively; P < 0.001). There was no effect of eST on T-cell subset percentages.

The proliferative response of T and B cells to Con A, PHA, and PWM (P = 0.17, 0.17, and 0.13, respectively; Figure 3) was not affected by eST.

There was no age effect in control horses in primary antibody response to KLH (Figure 4). There was an age × treatment interaction in primary antibody response to KLH antigen. Aged mares treated with eST displayed lower mean peak antibody response (d 17) relative to control mares of both age groups (P < 0.05). Young
Changes in weekly plasma IGF-I levels. Closed symbols denote eST-treated mares; open symbols denote vehicle-treated mares. Asterisks indicate the level of statistical difference: *P < 0.05; ***P < 0.001. Insulin-like growth factor-I was higher in eST-treated mares. There was an age \times treatment interaction on wk 5, 6, and 8.

Discussion

Because nutrition plays a crucial role in immune function and inadequate nutritional status may confound the relationship of aging and immune response (Krause et al., 1999), the nutritional status of all mares was assessed preceding the experiment and was monitored throughout the study. Diets were formulated based on NRC (1989) guidelines with additional consideration of alterations in dietary requirements due to age and somatotropin administration. Body weight values remained constant during the study, and minimal alterations were made to individual diets.

In mice, immune responsiveness was shown to vary with different phases of the estrous cycle (Krzych et al., 1978). In order to remove potential variability due to asynchronized estrous cycles in mares involved in the current study, all horses were injected with PGF₂α initially, and were given oral progesterone daily throughout the experiment. Although some of the horses began or continued to cycle during the study, further analysis of the data suggested that these phenomena did not affect the immune parameters tested.

Immunosenescence refers to the phenomenon of immune function deterioration with advancing age, leading to increases in susceptibility to infectious disease, cancer, and autoimmune conditions (Solana and Pawelec, 1998). Age-dependent alterations in various components of the immune system have been reported in humans and rodents (Miller, 1995). Recent research has also suggested that somatotropin and IGF-I, known to decline with advancing age (Corpas et al., 1993), act as cytokines with potential stimulatory effects on cells throughout the immune system in humans (Corpas et al., 1993) and monkeys (LeRoith et al., 1996).
We found no change in monocyte number with aging, in agreement with several studies (reviewed by Rink et al., 1998). Although increases in neutrophils—with no changes in eosinophils or basophils leading to overall increases in granulocyte number with aging—have previously been reported in humans (Cakman et al., 1997), we observed no increase in granulocyte number in aged horses. Examination of functions and responses of cells of the cellular innate component of the immune system was outside of the scope of this project. However, our findings suggest that reductions in cell number would not account for age-related deficiencies in the innate cellular immune function in horses that may be characterized in future studies.

The adaptive component of the immune system is particularly susceptible to the deleterious effects of aging in humans (Pawelec et al., 2000). Aged humans and most animals studied showed a significant decline in immune response primarily caused by changes in T cell immunity (Solana and Pawelec, 1998). Several studies have been conducted on components of T cell immunity in order to characterize the nature of observed declines. Recent studies of immunosenescence in humans (Wikby et al., 1998), rodents (Miller et al., 1997), and horses (Malinowski et al., 1997) have concentrated on quantifying T cells and on defining shifts in the number and percentage of T cell subsets. Lymphocyte proliferation and cytokine production have also been extensively examined to further characterize the effects of aging on T cell function. In agreement with data collected in humans (Inkeles et al., 1977; Krishnaraj et al., 1998), we found no difference in the number of peripheral blood lymphocytes with age. However, we did observe an age effect on lymphocyte subset populations. We found a significantly higher percentage of CD4+ lymphocytes and a lower percentage of CD8+ lymphocytes or a higher CD4:CD8 ratio in aged horses, in agreement with data reported for humans and mice (Komuro et al., 1990; Utsuyama, et al., 1992). Several studies have examined lymphocyte subsets, namely, CD4+ helper and CD8+ cytotoxic T cells in cells from aged horses (Moody et al., 1981; Masoro 1988; Grossmann et al., 1989; Matour et al., 1989; Utsuyama et al., 1992). The analysis of CD4+ cells from animals depleted of peripheral populations and reconstituted with young precursors has shown that the new CD4+ T cells in the aged host animals were predominately memory-like, suggesting that the aged microenvironment drives an accelerated maturation of naive CD4+ T cells to a memory state (Solana and Pawelec, 1998).

In agreement with data collected in studies with humans (Crisi et al., 1998), we found a lower percentage of CD8+ peripheral blood lymphocytes in aged mares. Decreases in CD8+ T cells have been attributed to a decrease in virgin CD8+ T cells in peripheral blood lymphocytes (Crisi et al., 1998); CD8+ cytotoxic T lymphocytes play a major role in protection and recovery from viral infections and are important in immune surveillance and determination of the outcome of reactivation of latent viruses (Slater and Hannant, 2000). Cakman et al. (1996) reported age-related reductions in IFN-γ secretion due to reductions in cytokine-producing CD8+ subpopulations in humans. A lower percentage of CD8+ subset numbers has been further suggested as an important reason for the emergence of autoimmune-based disease in elderly humans (Nagel et al., 1981).

In addition to shifts in T lymphocyte subsets, a decrease in the proliferative ability of existing T cells has also been implicated in the characterization of the
observed immunosenescence in older humans (Pawelec and Solana, 1997). The age-related impairment of T cell functions include a decrease in cytotoxic T cell synthesis (Weksler, 1983) as well as an impairment of mitogenic stimulation of T lymphocyte subsets and a decrease in the ability of circulating T lymphocytes to proliferate in response to in vitro mitogenic stimulation in aged humans (Matour et al., 1989; Inkeles et al., 1977).

Reduced lymphocyte responses to concanavalin A and phytohemagglutinin and pokeweed mitogen in aged horses have been reported (Horohov et al., 1999). Matour et al. (1989), reported that mean mitogen-induced proliferation in elderly people was 50% of the response of young people, with 8% of the elderly subjects exhibiting less than 10% of the response of young subjects. Contrary to previous results reported by our laboratory, we did not observe significant age-related differences in mean mitogen-stimulated lymphocyte proliferative response and have attributed our current results to a smaller sampling population.

Studies investigating the effects of age on humoral immune response have demonstrated that primary immunization with T cell-dependent protein antigens such as keyhole limpet hemocyanin induces antibodies within the IgG1 and IgG3 subclasses in elderly humans (De Greef et al., 1992). We examined the ability of young and aged horses to mount a humoral response to a novel antigen, namely, KLH. In agreement with data in mice (Borghesi et al., 1995), we found no differences between the ability of young and aged horses to mount a primary antibody response to antigen. Our results, coupled with data regarding secondary antibody response to equine influenza virus (Horohov et al., 1999), suggest that horses resemble other species with regard to age-related alterations in humoral response.

Characterization of age-related impairments of immune function in a variety of species have led to research using somatotropin in attempts to reverse immunosenescence. Older, mature horses have lower insulin-like growth factor-I concentrations when compared with young, growing horses (Malinowski et al., 1996). In agreement with our previous studies conducted in horses, we observed an increase in IGF-I concentrations with eST treatment in young and old mares,

![Figure 4](image.png)

**Figure 4.** Mean primary antibody response to KLH antigen. Aged eST-treated mares (■) displayed lower peak (d 17) antibody response compared with control mares (□; *P < 0.05). Young eST-treated mares (●) displayed higher peak antibody response compared with control mares (○; *P < 0.05). Peak primary antibody response was higher in young eST-treated mares (●) compared with aged mares treated with eST (■; ***P < 0.001).
confirming the efficacy of the recombinant hormone. We also found a greater proportional increase in the concentration of IGF-I relative to pretreatment values in aged mares treated with eST when compared with young treated mares, suggesting a possible increased sensitivity to ST or a decrease in clearance rate of ST or IGF-I in the older animals.

In agreement with Goff et al. (1991), we observed no significant change in lymphocyte number with eST administration in young mares. Lymphocyte number was lower in aged mares treated with eST when compared with control aged mares and young mares, suggesting a drug effect on cell trafficking or clonal expansion.

In a recent study, recombinant human growth hormone (rhGH) increased Con A-induced DNA synthesis in vitro, and recombinant human IGF-I (rhIGF-I) decreased peripheral blood CD4:CD8 ratio in aged female monkeys (LeRoith et al., 1996). In horses, the alterations in CD4+ and CD8+ counts we observed were not affected by somatotropin administration. It has been reported that somatotropin augments antibody synthesis in vivo and increases lectin-induced T cell proliferation and interleukin-2 synthesis in vitro (Kelly, 1990b).

Contrary to data collected in monkeys (LeRoith et al., 1996), heifers (Elvinger et al., 1991), and humans (Kelley, 1990a), we observed no enhanced proliferative response to mitogens in mares treated with eST. By contrast to previous reports in other species, our findings suggest that equine lymphocytes may be resistant to the stimulatory effects of ST.

Both rhGH and rhIGF-I increased in vivo (antibody titer to tetanus toxoid) responses by lymphocytes in monkeys (LeRoith et al., 1996). We observed an increase in antibody response to KLH with eST treatment in young horses, suggesting a stimulatory effect. In contrast to reported effects of rhGH on antibody response in aged monkeys, primary antibody response was lower in eST-treated aged female horses, suggesting a suppressive effect on B cell function or isotype switching. However, the mechanism involved with the reduced primary antibody response of aged horses treated with eST was beyond the scope of this experiment. It has been shown that IGF-I at approximately physiologic concentrations will potently suppress both the proliferation of lymphocytes and the generation of antibody-producing cells. High levels of unbound IGF might otherwise result in chronic immune suppression in mice (Hunt et al., 1986). Christensen et al. (1996) concluded that equine somatotropin administration, in aged horses, resulted in a sustained increase in blood plasma insulin and IGF-I and also magnified the normal postprandial response of insulin to feeding. Therefore, an exogenous somatotropin-induced elevation of insulin and IGF-I may be responsible for the impairments observed in this study.

In conclusion, horses share several of the characteristics of immunosenescence observed in a variety of species. However, eST does not reverse immunosenescence in horses.

Implications

There is a general agreement that an observed age-related increase in the incidence of illness and disease as well as an increase in severity and a greater risk of certain infections, malignancies, and autoimmune disease are due to deficiencies in immune surveillance. Horses over 20 yr of age constitute approximately 15% of the horse population, many of which remain involved in breeding programs and athletic activities. Characterization of changes in immune function of aged horses may lead to alterations in vaccination strategies to enhance the protection of this population. On the basis of our characterization of some of the effects that aging has on immune function, we believe that aged horses would benefit from therapies capable of restoring immune function. However, somatotropin may induce physiologic changes that suppress certain components of immune function directly or through mediators.

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