DECREASED ADAPTIVE AND INFLAMMATORY RESPONSES AS A CONSEQUENCE OF AGING CONTRIBUTE TO INJURY AND SICKNESS RESPONSE IN A RAT MODEL OF WMSD.

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Aims

1. To determine the extent to which exposure to a high repetition low force task causes injury, inflammation or degenerative responses in tissues of aged rats.
2. To determine the extent to which exposure to a high repetition low force task causes sensorimotor or psychosocial behavior dysfunction in aged rats.

Methods

Twenty-nine aged (17 months of age) Sprague-Dawley rats were divided into 3 groups: high repetition low force (HRLF, n=14), trained controls (TC; initial shaping only; age-weight matched, n=7), or normal controls (NC; age-matched; n=8). Also, 21 young adult rats were divided into 3 groups: HRLF (n=9), TC (n=6), and NC (n=10). For the HRLF task, rats were cued with an auditory stimulus every 15 sec. to reach and pull a handle attached to a tension-compression load cell and to exert a force of 15% maximum voluntary pulling force for a minimum of 50 msec. Force output was digitally sampled throughout each session. Rats performed the task for 2 hrs/dy in 4, ½ hr sessions separated by 1½ hr breaks and for 3 dys/wk. Forepaw sensation, grip strength, and social interaction (with juvenile rats) were measured in weeks 3 and 6 and compared to baseline by repeated measures ANOVA. At weeks 3 and 6, subgroups of rats were euthanized (sodium pentobarbital 120 mg/kg body weight) for examination of serum and tissues as follows: serum was assayed for collagen type I and II (C1,2) cleavage, a marker of collagen degradation; pro-collagen II C-propeptide (CP II), a marker of collagen synthesis; and 11 cytokines/chemokines, markers of inflammation. Results were compared to serum collected from control groups using ANOVA. Forelimb flexor muscles were excised and examined using either molecular or protein assay techniques. RNA was extracted using Trizol (Invitrogen). Samples were hydrolyzed individually to Affymetrix Genechip arrays. Raw gene chip data were analyzed (Gene Sifter program) using log transformation, ANOVA, and ontological grouping by function.

Results

There were significant declines in paw sensation in week 3, and declines in social interaction by week 6, but not grip strength, in aged rats performing the HRLF task compared to aged controls. Serum markers of collagen degradation, collagen synthesis, and their ratio were not elevated in aged rats with task performance. However, serum levels of several cytokines and chemokines were affected either by task performance or age. Aged rats had increased serum MIP3a, IL-1beta and IL-6 by week 3 compared to aged controls; and increased IL-1alpha compared to young rats. In young rats, task performance lead to increased serum IL-1beta, TNF-alpha, MIP2, MIP3a, and IL-10 by week 6. IL-10, a key anti-inflammatory cytokine, did not increase in aged rats with task performance. In muscle, several genes related to adaptation down-regulated in aged rats compared to young rats, but upregulated in young rats with task performance. Many inflammation related genes upregulated in both young and aged rats with task performance, although others linked to inflammation modulation pathways down-regulated in aged rats. Degeneration related genes, e.g. DNA fragmentation factor beta, upregulated in aged rats, but down-regulated in young rats with task performance.

Conclusions

These findings are consistent with a dose-dependent onset of a systemic inflammatory response and tissue pathology, with performance of repetitive and forceful reaching and pulling. Some adaptive responses decreased while inflammatory responses increased in aged rats, perhaps explaining the development of behavioral declines suggestive of sickness behaviors.