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PERFORMANCE OF A REPETITIVE TASK BY AGED RATS LEADS TO MEDIAN NEUROPATHY AND SPINAL CORD INFLAMMATION WITH ASSOCIATED SENSORIMOTOR DECLINES

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Abstract—Epidemiological studies have demonstrated a relationship between advancing age and susceptibility to risk factors for median neuropathies and musculoskeletal disorders. In this study, we determined if performance of a voluntary reaching task by aged rats induced sensorimotor declines, median nerve dysfunction and increased inflammatory cytokines in peripheral nerves, muscle and spinal cord neurons. Aged (14 mon) rats were trained for 15 min/day for 4 weeks to learn a high repetition, low force (HRLF) task (19 reaches/min; 15% maximum pulling force). Aged task rats performed the task for 2 h/day, 3 days/wk, for 12 weeks (until they were 18 mon of age). No behavioral changes were detected in normal controls (NC) or food-restricted controls (FR C) as they aged. However, grip strength declined in HRLF rats in weeks 6–12 ($P<0.01$ each) and 12-week trained-only rats (TR; $P<0.05$), compared to NC. Mechanical hypersensitivity was present in weeks 9 and 12 HRLF reach limb forepaws ($P<0.01$ and $P<0.05$, respectively), and 12-week HRLF support limb forepaws ($P<0.01$) and hindpaws ($P=0.03$), compared to NC. By week 12, median nerve conduction velocity declined 23%, bilaterally, in HRLF ($P<0.001$ each), and 13% in TR ($P<0.05$), compared to NC. Tumor necrosis factor alpha (TNFα) increased in 12-week HRLF muscle ($P=0.005$), median nerve ($P<0.01$), and neurons in superficial lamina of HRLF cervical spinal cords ($P<0.01$), compared to NC. interleukin 1 beta (IL1β) also increased in superficial lamina neurons ($P<0.01$). Loss of grip strength was correlated with median nerve conduction slowing ($r=0.70$) as well as increased nerve and muscle TNFα ($r=-0.38$ and $r=-0.41$, respectively); decrease in forepaw withdrawal thresholds was correlated with median nerve conduction slowing ($r=0.81$), increased nerve TNFα ($r=-0.59$), and increased TNFα and IL1β in neurons in spinal cord dorsal horns ($r=-0.52$ and $r=-0.47$, respectively). Thus, aged rats performing a repetitive task exhibited sensorimotor declines that were associated with decreased median nerve conduction, and increased pro-inflammatory cytokines in the median nerve and cervical spinal cord neurons. **© 2010 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: aging, neuropathy, neuritis, repetitive task, work-related-musculoskeletal disorders, sensorimotor.

Median neuropathy, such as carpal tunnel syndrome, can result from mechanical trauma such as shear or compressive forces on the nerve, particularly if repeated, and has been linked to risk factors such as gender (female), advanced age (older), and reduced fitness (Bernard, 1997; Nathan et al., 1998; de Zwart et al., 2001; Diao et al., 2005; Zambelis et al., 2010). Patients with median neuropathy report symptoms such as pain in the hands/wrists or fingers that may travel into the forearm, elbow and shoulder, as well as paresthesias, numbness and weakness (Gerr et al., 2002). An objective diagnosis of median nerve dysfunction is typically based on electrophysiological evidence of slowed median nerve conduction localized to the wrist, although the combination of electrodiagnostic findings and symptom characteristics are reported as providing the most accurate diagnosis of carpal tunnel syndrome (Rempel et al., 1999; Rempel and Diao, 2004; Diao et al., 2005).

Other risk factors for the development of neuropathies as well as several other types of musculoskeletal symptoms (MSS) and disorders (MSDs), such as radicular pain, somatic pain, myalgesias, tendinitis and tendinopathies, include performance of jobs characterized by repetitiveness, forcefulness and awkward postures (Bernard, 1997; Szabo, 1998; Gerr et al., 2002; Bonfiglioli et al., 2006, 2007; Zambelis et al., 2010). A relationship between advancing age and susceptibility to other risk factors for neuropathies and types of MSS/MSDs has also been reported (BLS, 2009; Gerr et al., 2002; Ratzlaff et al., 2007; Zambelis et al., 2010), although one longitudinal study suggests that slowing of conduction in the median nerve occurs naturally with increasing age (Nathan et al., 1998). Epidemiological data show that the incidence rate of lost workday injuries and illnesses due to repetitive motion is 1.6 times higher in workers aged 55–64 compared to those aged 25–34 (BLS, 2009). Computer operators over age 30 show increasing risk of developing neck, shoulder, arm and hand symptoms, such as pain, aching, burning, numbness or tingling, in a 3-year prospective study of MSS/MSD incidence in newly hired workers in computer intensive jobs, with the most common disorder being somatic pain syndrome (Gerr et al., 2002). Our laboratory has reported that patients with upper extremity MSS/MSDs have in-

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Abbreviations: FR C, food-restricted controls; HRLF, high repetition low force; MPF, maximum voluntary pulling force; MSDs, musculoskeletal disorders; MSS, musculoskeletal symptoms; TR, trained-only rats.

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creased frequency of local signs of pain and tenderness, peripheral nerve irritation and weakness as well as increased frequency of these symptoms at multiple anatomical sites (mean age=45; range of 19–74, with 23 of 31 subjects over 30), findings that interestingly correlated with increased serum inflammatory cytokines (Carp et al., 2007).

Recent work in animal models suggests that performance of repetitive tasks induces median neuropathies, hand movement dysfunctions, and inflammatory tendinopathies (Topp and Byl, 1999; Barbe et al., 2003; Clark et al., 2003, 2004; Perry et al., 2005; Sommerich et al., 2007; Coq et al., 2009; Fedorczyk et al., 2010). Using a unique model of upper extremity MSD, we have reported that in young adult rats repetitive reaching and grasping for 8–12 weeks leads to degraded myelin, increased macrophages and cytokines, decreased nerve conduction velocity, and increased collagen deposition in the median nerve, as well as persistent inflammation in musculoskeletal tissues, woven bone formation, tendon disorganization and fibrosis, and myofiber fray (Barbe et al., 2003, 2008; Barr et al., 2004; Clark et al., 2003, 2004; Al-Shatti et al., 2005; Elliott et al., 2009b; Coq et al., 2009; Fedorczyk et al., 2010; Rani et al., 2009, 2010). These tissue changes were associated with sensorimotor declines, including reduced reach performance, decreased grip strength and changes in forepaw sensation (Barbe et al., 2003, 2008; Clark et al., 2003, 2004; Elliott et al., 2009a,b; Fedorczyk et al., 2010; Rani et al., 2010). The declines in median nerve conduction were exposure-dependent, ranging in reductions of 9–17% depending on the level of task intensity (Clark et al., 2003, 2004; Elliott et al., 2009b). We have also reported that neurochemicals involved in nociception were increased in the dorsal horns of cervical spinal cord segments with performance of repetitive tasks in young adult rats and that this increase in neurochemicals was associated with nociceptive-like behaviors (Elliott et al., 2008, 2009a,b). However, we have yet to determine if similar changes are induced in aged rats performing repetitive tasks.

Evidence that inflammatory responses in the peripheral and central nervous systems are associated with cutaneous hypersensitivity is documented in acute animal models of peripheral nerve injury (DeLeo et al., 1997; Chacur et al., 2001; Gazda et al., 2001; Milligan et al., 2003; Kelly et al., 2007). In particular, increased pro-inflammatory cytokines at the spinal cord level have been implicated in the development of cutaneous hypersensitivity in studies of cryoneurolysis, chemical insult, crush or ligature-induced chronic constriction nerve injuries in young adult rodents (DeLeo et al., 1997; Hunt et al., 2001; Winkelstein et al., 2001b; Rutkowski et al., 2002; Hubbard and Winkelstein, 2005; Svensson et al., 2005; Rothman and Winkelstein, 2007; Hatashita et al., 2008). However, an association between cutaneous hypersensitivity and a central inflammatory response has yet to be investigated in a model in which nerve dysfunction is induced by long term performance of a voluntary repetitive task.

Therefore, in this study we extended our model to aged rats performing a high repetition low force (HRLF) task. We tested the hypothesis that performance of this repetitive task by aged rats induces sensorimotor declines that are associated with peripheral nerve dysfunction and inflammation at levels similar to those observed in young rats in our previous studies (Al-Shatti et al., 2005; Clark et al., 2003, 2004; Elliott et al., 2009a). We also examined, for the first time, whether there were repetitive task-induced inflammatory changes in neurons in cervical spinal cord dorsal horns. Mechanical sensation in the hindpaws, limbs not involved in performing the repetitive task, was also examined to determine if extraterritorial cutaneous mechanical hypersensitivity was present. Moreover, since grip strength declines can be induced by intramuscular injections of pro-inflammatory cytokines (Schafers et al., 2003a; Beyreuther et al., 2007), we examined forelimb muscles involved in gripping (flexor digitorum muscles) for inflammatory cytokine levels to determine whether any task-induced increases of muscle cytokines were associated with decreases in grip strength.

EXPERIMENTAL PROCEDURES

Animals

All experiments were approved by the Institutional Animal Care and Use Committee in compliance with NIH guidelines for the humane care and use of laboratory animals. Studies were conducted on a total of 56 aged, female Sprague–Dawley rats (14 mon at onset of task training; 18 mon at euthanasia). Adult female rats were used for several reasons: (1) Human females have a higher incidence of work-related MSS/MSDs than males (de Zwart et al., 2001; Gerr et al., 2002; Wijnhoven et al., 2006); (2) we have used young adult female rats in extensive studies using this model, consequently our database is relevant to female rats and for comparison purposes, we prefer to continue with this gender; and (3) the examination of male rats, which are both larger and stronger, would require adjustments in operant conditioning equipment, including a switch to higher capacity force transducers, as ours were chosen for their sensitivity to the force generating capabilities of adult female rats. Rats were housed individually in the central animal facility in transparent plastic cages in a 12 h light: 12 h dark cycle with free access to water.

Thirty-eight rats were food restricted to within 5% of their naive weights. Thirty-four went through an initial training period of approximately 4 weeks, in which they were trained to perform the reaching and handle pulling task (see training regimen below). Eighteen of these trained rats then went on to perform a HRLF task (see task regimen below). The remaining 16 trained rats, serving as trained-only rats (TR), did not proceed past week 0 to the task regimen, but rested 12 weeks until euthanasia at time points matched to HRLF rats. The remaining four food restricted rats were not trained, and served as food-restricted controls (FR C). Eighteen more rats served as age-matched normal controls (NC) with free access to food. The NC rats did not undergo food restriction, training or task performance.

All rats were weighed at least weekly throughout the experiment and food adjusted accordingly. In addition to food pellet rewards, all rats received Purina rat chow daily. TR and FR C rats received daily allotments of food pellets and rat chow matched to the HRLF rats. NC had free access to food. All rats were inspected weekly and again post-mortem for presence of illness or tumors. As a consequence, an additional eight rats were eliminated from the study due to age-related health issues, such as renal failure, presence of tumors or mortality. Additional sentinel rats were examined for presence of viral infections as part of the regular veterinary care (no viruses were detected).

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