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Tissue pathophysiology, neuroplasticity and motor behavioural changes in painful repetitive motion injuries

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1. Introduction

Therapeutic interventions in repetitive motion disorder have focused primarily on the musculoskeletal tissues of the “exposed” body parts. Yet, many patients experience persistent symptoms and chronic disability in spite of treatment of localized tissue injury. Work with an *in vivo* model in the rat to determine both the nature of tissue pathophysiology and the dose-response relationship between repetition-force and tissue pathophysiology has provided insight into such systemic and nervous system effects.

2. Methods

Rats are trained to reach and grasp a small food pellet or a force handle, in which case they pull at a target force threshold to obtain a food pellet reward, for 2 h/day, 3 days/week. Four repetition-force protocols have been used: high repetition-high force (**HRHF**; 8-12 reaches/min, 60% maximum grip strength), high-repetition-low force (**HRLF**; 8-12 reaches/min, <15% maximum grip strength), low repetition-high force (**LRHF**; 4-6 reaches/min, 60% maximum grip strength) and **LRLF** (4-6 reaches/min, <15% maximum grip strength).

Reach rate, task duration (the amount of time per day the animals are willing to participate in the task), grip strength, paw sensation, and grooming skill are monitored. Nerve conduction velocity (NCV) is determined for the median nerve. Tissues and serum are examined for evidence of injury, inflammation and fibrosis. Spinal cord and somatosensory cortex have also been examined for evidence of neuroplasticity.

3. Review of results

Evidence of tissue injury includes decreased median nerve **NCV** in the **HRLF**, **HRHF**, and **LRHF** groups by 12 weeks, which is accompanied by decreased grip strength and paw sensation. These findings are indicative of carpal tunnel syndrome (Clark et al., 2003,2004). Myotendinous fibrillation is evident as early as 6 weeks of **HRLF** task performance, and is accompanied by infiltrating macrophages (Barbe et al., 2003). Cortical bone at sites of tendon or ligament attachments undergoes degradation by osteoclasts and formation of woven bone (Barr et al., 2003), a pathological finding in the mature skeleton.

Macrophage infiltration is evident in many tissues, including tendon, connective tissue, muscle, and peripheral nerve, and is found in the distal as well as the proximal forelimb (Barbe et al., 2003; Barr et al., 2003; Barr and Barbe, 2004). The macrophage response is dose-dependent

(**HRHF** > **HRLF** > **LRLF**) with respect to number of infiltrating cells and time to resolution of the response. The macrophage response extends to the contralateral, nonreach limb and the hindlimb (Barr et al., 2004). The production of pro-inflammatory cytokines by several cell types also accompanies the macrophage response. In addition, IL-1 alpha is upregulated in the serum of **HRLF** animals by 8 weeks, suggesting a systemic inflammatory response. Fibrosis is evident in and around the median nerve after 12 weeks of the **HRLF** and **HRHF** tasks (Clark et al., 2003, 2004). Changes to the spinal cord are bilateral, with upregulation of substance P and its receptors in the superficial laminae of the bilateral dorsal horns by 5 weeks.

Reach rate is maintained throughout the first 6 weeks in the **LRLF** group, it declines in week 6 in the **HRLF** and **LRHF** groups, and declines in weeks 3 and 6 in the **HRHF** group. Grip strength also declines in the **HRLF** and **HRHF** groups (Clark et al., 2003,2004). Animals develop an uncoordinated, raking movement pattern regardless of task level, but the **LRLF** group exhibits this behaviour to a lesser degree. This movement pattern is associated with prolonged reach time and difficulty manipulating and eating small food pellets (Barbe et al., 2003;Barr et al., 2002). Finally, there are several behavioural outcomes that indicate a sickness response in our model (Dantzer, 2004). Task duration is accompanied by somnolence and decreases in a dose-dependent manner. Decreased grooming skill is accompanied by an increased frequency of non-responses rather than a degradation of forelimb function. This type of behavioural withdrawal is similar to the types of behaviours noted in other animal models of acute infection or cytokine-mediated illness (Watkins and Maier, 1999;Dantzer, 2004).

4. Conclusions

This model shows the effects of repetitive and/or forceful movements of the upper limb on tissues and on behaviour. Findings show that cumulative exposure to this task causes tissue and behavioural responses consistent with repetitive strain injury. The primary tissue response is inflammatory and appears to be mediated by inflammatory cells and proinflammatory molecules within the first 3-8 weeks, although the inflammatory response is dependent on tissue type and task exposure, declining with lower task demands. There is a resolution of the cytokine response in the **HRLF** and **LRLF** groups despite continued task performance (although macrophages continue to increase in some tissue types through week 12 in the **HRLF** group).

Progressive degradation of motor performance is evident among animals at high exposure levels. In addition to loss of motor performance ability, animals performing the HR and/or HF tasks exhibit sickness behaviours. These findings show a complex bio-psychosocial response to the performance of highly repetitive and/or forceful tasks that may be mediated by the immune system through a widespread inflammatory mechanism (Barr et al., 2004). These findings provide evidence for a highly complex response to the performance of highly repetitive motions that involves not only the exposed peripheral tissues, but also somatosensory and affective as well as regulatory structures of the central nervous system. Clinicians should refocus treatment to encompass all of the tissues and systems affected by repetitive motion disorders.

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