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The pathogenesis of inflammatory muscle pain

Loram, Lisa Carole

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ABSTRACT

The aim of my thesis is to further investigate the mechanisms underlying inflammatory muscle pain. Despite numerous studies investigating the mechanisms of inflammatory hyperalgesia, little is known of the mechanisms underlying inflammatory muscle hyperalgesia. Using rats as experimental animals, I investigated inflammatory hyperalgesia in muscle and compared it to that of inflamed cutaneous tissue. I injected carrageenan, a plant-origin polysaccharide, into leg muscle and into the hind paw of rats, and measured the behavioural response, as well as cytokine changes, in both plasma and inflamed tissue. Carrageenan induced inflammatory hyperalgesia but the cytokine cascade was not the same in muscle and cutaneous tissue. At no time following carrageenan injection was muscle tumour necrosis factor alpha (TNF-α) concentration elevated above that of muscle injected with saline. TNF-α is a key inflammatory mediator in cutaneous tissue, but apparently not in muscle. Interleukin-1β (IL-1β) and interleukin-6 concentrations also were different during muscle inflammation compared to those of cutaneous inflammation. IL-1β and IL-6 concentrations, following carrageenan injection, were elevated later in muscle compared to in cutaneous tissue. IL-1β is a potent sensitizer of nociceptors in cutaneous tissue, and also may play an important role in sustaining muscle pain, but it is unlikely to be an initiator of the inflammatory muscle hyperalgesia. In the course of comparing muscle hyperalgesia and cutaneous hyperalgesia, I aimed to identify whether these differences in cytokine concentrations were unique to muscle tissue or if similar differences in cytokine concentrations existed between the hind paw and other cutaneous sites. To explore an alternative cutaneous tissue site, I injected carrageenan into the rat tail and measured the behavioural response, changes in cytokine concentrations and histological changes. Elevations of pro-inflammatory cytokines occurred concurrently with the infiltration of

leukocytes into the inflamed tail tissue with the thermal and mechanical hyperalgesia similar to that found in the hind paw. Different mechanisms therefore appear to underlie muscle and cutaneous inflammatory hyperalgesia, regardless of the site used to investigate cutaneous inflammation. One of the consequences of the poor understanding of muscle pain is the lack of a reliable regimen for treating human muscle pain, including delayed-onset muscle soreness (DOMS). DOMS, which has a partial inflammatory pathogenesis, is not relieved by non-selective cyclo-oxygenase inhibitors. This phenomenon may be that prostaglandins are not produced peripherally or centrally, when muscle tissue is damaged. I investigated the effect of inhibiting cyclo-oxygenase-2, the isoform released during inflammation, on DOMS in human volunteers. I found that rofecoxib, a cyclo-oxygenase-2 inhibitor, did not attenuate DOMS and nor did tramadol, a central-acting analgesic. The neurochemical pathway underlying DOMS therefore appears to be distinct from the pathways which underlie pain and hyperalgesia in other syndromes. Future research should include investigations into the central mechanisms of muscle pain and blocking the action of IL-1β and CINC-1 both peripherally and centrally may prove a beneficial target for the treatment of clinical muscle pain.