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BRAIN RESEARCH

Research Report

Diclofenac exerts local anesthetic-like actions on rat masseter muscle afferent fibers

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ABSTRACT

The use of topical non-steroidal anti-inflammatory drugs, such as diclofenac, for the treatment of temporomandibular disorders-related myofascial pain is based on the premise that their analgesic effect is mediated by a local action on the excitability of muscle nociceptors, despite a lack of muscle inflammation in these patients. To investigate if diclofenac has an effect on muscle afferent fibers in the absence of inflammation, *in vivo* recordings of the response of masseter muscle afferent fibers to mechanical and noxious chemical (hypertonic saline) stimulation were made in anesthetized Sprague–Dawley rats. It was observed that injection of diclofenac (0.1 or 1 mg/ml) alone could elevate afferent mechanical threshold for a 10 min period post-injection. Hypertonic saline-evoked afferent discharge was also significantly attenuated by the higher concentration of diclofenac and lidocaine (20 mg/ml), but not by the lower concentration of diclofenac. Additional experiments were undertaken to investigate whether activation of ATP-sensitive potassium (K_{ATP}) channels could contribute to the effects of diclofenac. The K_{ATP} channel opener pinacidil (0.1 mg/ml) significantly enhanced potassium chloride-evoked afferent discharge consistent with the concept that masseter afferent fibers have functional K_{ATP} channels, however, subsequent experiments indicated that diclofenac (1 mg/ml) significantly suppressed potassium chloride-evoked afferent discharge and that pinacidil did not affect hypertonic saline-evoked afferent discharge. These results indicate that diclofenac can exert a "local anesthetic-like" action on masseter afferent fibers in the absence of inflammation, but that this effect does not appear to involve the opening of K_{ATP} channels.
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1. Introduction

The most debilitating symptom of temporomandibular disorders (TMDs), which are suffered by an estimated 5–10% of the North American population, is pain in the temporomandibular joint and/or masticatory muscles (Carlsson and LeResche, 1995; Drangsholt and LeResche, 1999; Dao and LeResche, 2000; Fillingim and Maixner, 2000). Non-steroidal anti-inflammatory drugs (NSAIDs) are routinely used for the treatment of mild to moderate musculoskeletal pain arising from TMDs (Carlsson and LeResche, 1995; Drangsholt and LeResche, 1999). Although considered relatively safe drugs, chronic systemic administration of NSAIDs is associated with significant side effects (Gotzsche, 2000; McQuay and Moore, 2003). As a result,

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Abbreviations: TMDs, temporomandibular disorders; NSAIDs, non-steroidal anti-inflammatory drugs; COX, cyclooxygenase; ATP-sensitive potassium, K_{ATP}; HS, hypertonic saline; KCl, potassium chloride; CV, conduction velocity; MT, mechanical threshold; Analysis of variance, ANOVA; NMDA, *N*-methyl-D-aspartate; PGE2, prostaglandin E2; SUR, sulphonylurea receptor

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interest in topical NSAID creams or patches for the treatment of musculoskeletal pain has increased (Moore et al., 1998; Gotzsche, 2000). The use of topical NSAIDs for the treatment of TMD-related myofascial pain is based on the premise that the analgesic effect of this class of drug is mediated by a direct action on the excitability of craniofacial afferent fibers in the painful muscle and/or joint.

All currently available NSAIDs inhibit one or more of the isoforms of cyclooxygenase (COX), the rate limiting enzyme involved in the conversion of arachidonic acid to prostaglandins (Walker, 1995; Cashman, 1996; Gotzsche, 2000; Schaible et al., 2002). Although a number of other inflammatory mediators have been implicated in the increased sensitivity of joint and muscle afferent fibers (peripheral sensitization) under inflammatory conditions (Mense, 1977; Mense, 1982; Diehl et al., 1993; Mense, 1993; Schaible and Grubb, 1993; Graven-Nielsen and Mense, 2001; Schaible et al., 2002), the analgesic efficacy of NSAIDs in myositis and arthritis is currently thought to result from the ability of these drugs to inhibit the synthesis of prostaglandins at the site of tissue injury (Walker, 1995; Cashman, 1996; Gotzsche, 2000). However, it is uncertain whether any of these inflammatory mediators play a significant role in the development of masticatory muscle pain in TMDs since gross tissue damage and/or myositis are not common features of myofascial TMDs (Stohler, 1995, 1999). Furthermore, it appears that the analgesic properties of at least some NSAIDs can occur at concentrations which have little or no effect on COX activity (Gordon et al., 2002). It is, therefore, not clear if locally administered NSAIDs have an effect on muscle nociceptors in the absence of gross inflammation or what mechanism(s) could contribute to this effect.

Diclofenac is one of the best studied topical NSAIDs for the treatment of muscle pain including that arising from myofascial TMDs (Moore et al., 1998; Galer et al., 2000; Affaitati et al., 2001; Di Rienzo Businco et al., 2004). Behavioral studies in rats have suggested that a part of the diclofenac's peripheral analgesic mechanism may involve opening of ATP-sensitive potassium (K_{ATP}) channels (Ortiz et al., 2002; Alves et al., 2004). In the present study, *in vivo* recordings of afferent fibers that innervate the rat masseter muscle were employed to investigate whether intramuscular injection of the diclofenac alters the excitability of muscle afferent fibers through a local anesthetic-like mechanism that involves opening of K_{ATP} channels.

2. Results

2.1. *Effect of diclofenac on MT*

To investigate if diclofenac has an effect on muscle afferent fibers in the absence of gross inflammation, in initial experiments the response of masseter muscle afferent fibers to mechanical stimulation was assessed before and after the injection of diclofenac (1.0 or 0.1 mg/ml) and compared to the effect of vehicle (phosphate buffered isotonic saline). Diclofenac could elevate afferent MT within 1 min of injection for a period of 10 min post-injection (Fig. 1C). Overall, the increase in MT after injection of diclofenac 1 mg/ml was significantly greater than vehicle (Fig. 1D).

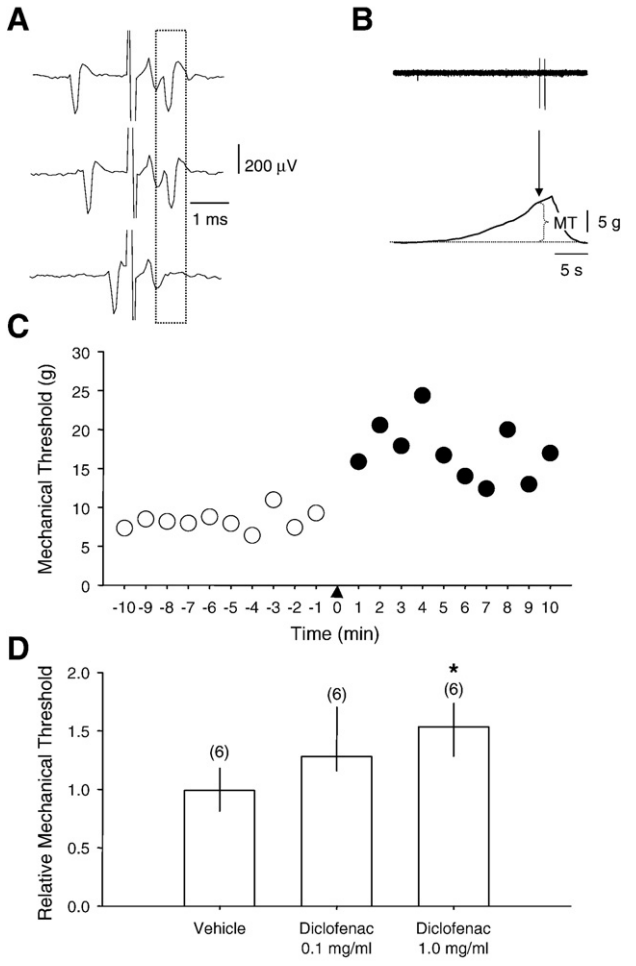

Fig. 1 – A. To confirm projection of the afferent fibers to the caudal brainstem, orthodromic action potentials evoked by mechanical stimulation of the masseter muscle (left side of stimulus artifact) were collided with antidromic action potentials (box). B. The line drawing shows an example of the measurement of MT with an electronic VF hair. C. The scatter plot illustrates the result of repeated mechanical threshold assessment before and after injection of diclofenac 1 mg/ml into the mechanoreceptive field of an Aδ fiber (CV 3.3 m/s) in a female rat. Note the increase in mechanical threshold for the 10 min period of assessment after injection of diclofenac. D. The vertical bar chart shows the median relative mechanical threshold for afferent fibers before and after vehicle or diclofenac. Although both concentrations of diclofenac increased afferent mechanical threshold compared to the vehicle, the increase was significant only for the 1 mg/ml concentration. Asterisk: $p<0.05$ Kruskal–Wallis ANOVA on ranks, Dunn's method. Error bars: interquartile range.

2.2. *HS and KCl-evoked afferent discharge properties*

To assess whether the effect of diclofenac on the MT of muscle afferent fibers might result from a local anesthetic effect of this drug, additional experiments to evaluate the effect of diclofenac on HS- and KCl-evoked afferent discharge were

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