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The Influence of Pain on Masseter Spindle Afferent Discharge

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Summary

Muscle spindles provide proprioceptive feedback supporting normal patterns of motor activity and kinesthetic sensibility. During mastication, jaw muscle spindles play an important role in monitoring and regulating the chewing cycle and the bite forces generated during mastication. Both acute and chronic orofacial pain disorders are associated with changes in proprioceptive feedback and motor function. Experimental jaw muscle pain also alters the normal response of masseter spindle afferents to ramp and hold jaw movements [1]. It has been proposed that altered motor function and proprioceptive input results from group III muscle afferent modulation of the fusimotor system which alters spindle afferent sensitivity in limb muscles[2]. The response to nociceptive stimuli may enhance or reduce the response of spindle afferents to proprioceptive stimuli. Several experimental observations suggesting the possibility that a similar mechanism also functions in jaw muscles are presented in this report. First, evidence is provided to show that nociceptive stimulation of the masseter muscle primarily influences the amplitude sensitivity of spindle afferents with relatively little effect on the dynamic sensitivity [3]. Second, reversible inactivation of the caudal trigeminal nuclei attenuates the nociceptive modulation of spindle afferents. Finally, functionally identified gamma-motoneurons in the trigeminal motor nucleus are modulated by intramuscular injection with algescic substances. Taken together, these results suggest that pain-induced modulation of spindle afferent responses are mediated by small diameter muscle afferents and that this modulation is dependent, in part, on the relay of muscle nociceptive information from trigeminal subnucleus caudalis onto trigeminal gamma-motoneurons. The implication of these results will be considered in light of current theories on the relationship between jaw muscle pain and oral motor function.

Keywords

Muscle spindle afferents; Masseter muscle; Pain; Proprioception; Rats

Introduction

Jaw muscle spindles have been particularly implicated in providing feedback necessary for interdental discrimination, mandibular positioning and possibly matching the spatiotemporal pattern of the moving jaw by modulating the output of the central pattern generator [4]. Pain influences jaw muscle proprioception and affects motor performance. Electrical stimulation of group III muscle afferents and intramuscular injections with hypertonic saline produces

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significant change in leg muscle gamma- fusimotor activity in animals [5,6]. These observations led Johansson and Sojka [2] to propose a “pathophysiological model” based on nociceptive modulation of the fusimotor system. According to their hypothesis, metabolites produced by (static) muscle contractions stimulate group III and IV muscle afferents, which in turn activate gamma-motoneurons that supply intrafusal fibers in both homonymous and heteronymous muscles, thereby influencing the spindle afferent discharge, spindle sensitivity, and proprioceptive feedback. The pathophysiological model has been evaluated primarily in spinally innervated muscles. Few studies have addressed nociceptive influences on proprioceptive afferents in jaw muscles. To address this gap we evaluated the effects of experimental muscle pain on spindle afferent responses to jaw opening movements, and on the modulation of fusimotor drive.

Jaw muscle spindles: morphological and functional differences

Evaluation of the pathophysiological hypothesis is warranted by the fact that jaw muscle spindles, and the nerves that supply them, differ in many ways from their spinal counterparts. Spindles are located primarily in jaw closing muscles. Since there are very few, if any, spindles in jaw opening muscles, the natural opposition between activity in agonist and antagonist muscles is lacking. Jaw muscle spindle intrafusal fibers are innervated by the trigeminal mesencephalic nucleus (Vmes), a centrally located population of primary afferents. In addition to making monosynaptic connections on trigeminal motoneurons, the central processes of the Vmes neurons contact numerous central targets (reviewed by Capra and Dessem [7]). The afferents supplying intrafusal fibers in jaw muscles are smaller in diameter than their spinal counterpart[8] and their conduction velocities are unimodally distributed.

Muscle spindle afferents may be categorized by their response to passive stretch as primary-like (with a distinct dynamic component), secondary-like (with a linear response to stretch), or as intermediate with properties of both. The dynamic response of primary-like spindle afferents is greatly enhanced by systemic injections of succinylcholine. Efforts have been made to classify jaw muscle spindle afferents in cats[9] and rats[10] by comparing the responses of spindle afferents to ramp and hold jaw opening before and after succinylcholine injection. These studies demonstrated masseter spindles in both species have a preponderance of intermediate type afferents.

General Methods

Extracellular recording experiments were performed to study the effects of nociceptive activation on jaw muscle spindle responses to ramp and hold jaw opening in anesthetized male *Sprague-Dawley* rats. Recordings were made either in Vmes or in the trigeminal motor nucleus (Vmot). In some cases, animals were paralyzed and artificially ventilated to identify either Vmes neurons or [11] Vmot neurons by electrical stimulation of the masseter nerve. The jaw was affixed to an electrodynamicometer to produce precisely controlled ramp openings and the mean firing rate (MFR) was assessed in response to repeated jaw opening cycles. Both the amplitude and velocity of jaw opening were varied to examine the static and dynamic response properties of the afferent. Injections of hypertonic saline (HS; 5%; 100 µl) were made into the mid-region of the masseter muscle. Intramuscular HS produces a robust activation of small diameter muscle afferents [12], elicits nocifensive responses in animals, and pain reports in humans [11], [13]. Isotonic saline (ISO) injections were used as a control and injection order was pseudorandomized. Additional details of experimental design and methods of analysis have been described previously [3].

Spindle afferent responses to intramuscular algescic injection

Small diameter muscle afferents in leg muscles act primarily through static fusimotor neurons to influence the response of group II spindle afferents [5,6]. Therefore, we proposed that nociceptive muscle afferents would differentially influence static fusimotor neurons to alter the static response to ramp stretch in jaw muscle spindle afferents[3]. Extracellular recordings from 43 Vmes spindle afferents were examined before, during and after intramuscular injection with HS. Units showing a clear dynamic component were classified as “primary-like”. Static behavior was assessed in 27 neurons (12 primary-like and 15 secondary-like) by comparing the MFR of each unit during open and hold phases at three different amplitudes of jaw openings. Dynamic behavior was assessed in 16 neurons by calculating the mean dynamic index of each “primary-like” unit in response to three different velocities of jaw opening. Linear regression analysis was used to obtain best fit lines to changes in MFR, before and after injection. The most common response to HS injection was a reproducible linear shift in the intercept of the amplitude response of spindle afferents with little change in slope. Interestingly, HS modulated units could show either increased or decreased activity to changes in amplitude (Figure 1a, b). Regardless of the direction of the shift, the response was consistent from trial-to-trial for a given unit. When tested, injections of HS into the contralateral muscle also produced changes that were similar both in direction and magnitude to those observed following ipsilateral injections. Significant changes in static behavior were observed in 75% (9/12) of “primary-like” units and 80% (12/15) of “secondary-like” units (units lacking a dynamic response) after HS injection ($P \leq 0.05$, paired t test). Five of the 16 units tested for changes in velocity sensitivity following HS showed significant changes in dynamic index ($P \leq 0.05$, paired t test). Neither the static nor the dynamic behavior of spindle afferents was changed following isotonic saline injection (Figure 1c). Injection of HS in a remote (limb) muscle also failed to alter jaw muscle spindle responses. The observation that HS injection predominantly altered the static response in jaw muscle spindle afferent is consistent with the notion that small-diameter chemosensitive afferents act on fusimotor neurons similar to previous reports in limb muscles.

Subnucleus caudalis contributes to nociceptive modulation of spindle afferent responses

Small diameter trigeminal afferents innervating jaw muscles terminate primarily in subnucleus caudalis (Vc) and in caudal subnucleus interpolaris (Vi)[14]. Algescic chemical stimulation of the masseter muscle reliably activates neurons in the trigeminal Vi that receive deep noxious inputs [12], and also alters proprioceptive processing of neurons in the medial edge of Vi and the adjacent parvicellular reticular formation [15]. Therefore it is possible that changes in spindle afferent response to noxious stimuli depend on input from caudal trigeminal nuclei. To test this idea, 36 Vmes muscle spindle afferents were identified using ramp and hold jaw openings. Twenty nine (81%) Vmes neurons in this study were modulated by HS saline (Figure 2). The response to HS injection of the modulated cells was studied before and five minutes after reversible inactivation of Vc; produced by injecting a small amount of lidocaine (1 μ l.; 4%) in the dorsolateral medulla just caudal to the obex. Lidocaine injections did not affect muscle spindle afferent responses to ramp and hold jaw opening. However, 5 minutes after lidocaine injection, 65 % of these units did not respond to reinjection with HS. We were able to record and retest 10 of these cells at one hour. Six of the 10 recovered their pre-lidocaine response to HS (Figure 2). These results support the idea that HS-induced changes in spindle afferent responses depends, in part, upon input from Vc. The fact that more profound reduction of HS modulation was not observed may be due to technical issues or the likelihood that some masseter nociceptive afferents provide axon collaterals to rostral trigeminal subnuclei [7].

Intramuscular hypertonic saline alters spontaneous discharge of gamma-motoneurons

Direct physiological evidence for fusimotor modulation by algescic chemical stimulation, was obtained by recording from Vmot to identify cells with properties characteristic of gamma-motoneurons. Using a combination of criteria described by Sessle and others [16–18], extracellular recordings were made from 26 putative gamma- motoneurons. These units had a moderate to high level of resting discharge (ranging from 5–51 imp/sec), were antidromically driven by stimulation of the masseter nerve, and were not directly modulated by passive jaw openings. After recording preinjection baseline neuronal activity, HS injections were made in the masseter to determine whether nociceptive stimulation modified the mean resting discharge. Of 26 putative gamma- motoneurons, 10 showed increased activity in response to HS, 10 showed reduced activity and six showed little or no change. The time course of the algescic influence lasted up to several minutes and was comparable in duration to the HS-mediated effects observed in spindle afferents. Vehicle injections were ineffective. Therefore, algescic substances can either enhance or inhibit the discharge of gamma-motoneurons and explain the bidirectional responses observed in muscle spindle afferents.

Discussion

Small diameter chemosensitive muscle afferents that project to Vc are capable of modulating spindle afferent responses. Algescic chemical injections of masseter muscle preferentially influences the amplitude sensitivity of jaw muscle spindle afferents consistent with actions on static gamma-motoneurons. According to the pathophysiological model, metabolites produced by muscle contractions activate group III and IV muscle afferents, which in turn activate gamma-motoneurons supplying intrafusal fibers in both homonymous and heteronymous muscles thus increasing the spindle stretch sensitivity and reflex-mediated muscle stiffness. Unlike “hyperactivity” or “vicious cycle” models, which predict increased muscle tone at rest, the pathophysiological model predicts increased muscle activity during voluntary motor activity but not at rest. Nevertheless, observations that algescic chemical stimulation produces both excitatory and inhibitory responses in fusimotor neurons and spindle afferents complicate predictions that accumulation of metabolites invariably leads to increased spindle sensitivity. Stimulation of group III muscle afferents, has been shown to produce either an activation or inhibition of static gamma- motoneurons [18,19] in limb muscles. This also seems to be the case for jaw muscles.

Oral sensory and motor function is altered in patients with temporomandibular Disorders (TMD) and myofascial pain. Patients with TMD show significant impairment in performing interdental discrimination and mandibular positioning tasks [20] and feedback from spindle afferents play an important role in these kinesthetic functions. Changes in motor behavior observed in orofacial pain conditions such as TMD include limited range of motion, decreased force of contraction, and irregular masticatory cycles. The changes in jaw muscle spindle afferent responses and gamma fusimotor neuron activity described in this report favor the existence of fusimotor modulation similar to that proposed by the pathophysiological model. However, the bidirectional responses to noxious stimulation may be more compatible with the predictions of the pain adaptation model [21] so that appropriate patterns of excitation and inhibition protect the injured muscle by subtle, yet coordinated, peripheral modulation of motor activity during mastication that act on specific elements of the pattern generator.

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Figure 1.

This figure shows representative responses of two spindle afferents to HS injection (a.) Ipsilateral HS injection altered the response of this unit as evidenced by a shift in the regression line and the increase in intercept (gain). The same result was obtained from contralateral injection with HS (b.) The regression line was shifted and the intercept was reduced in this unit indicating a reduction in amplitude responses to HS. (c.) Vehicle injection had no affect on the same cell presented in (a). Figure adapted from Masri et al, 2005, with permission.

Figure 2.

Intramuscular HS injection modulated 29 of 36 (81%) Vmes neurons. Lidocaine injection blocked the HS induced modulation in Vmes neurons. Five minutes after lidocaine only 10 (35%) of the 29 cells were modulated by HS injection (* $p \leq 0.05$, Chi-square). We were able to hold 10 cells of the 29 HS modulated Vmes units for one hour. Of these, 6 recovered their response to HS injection.