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Research report

Substance P does not play a critical role in neurogenic inflammation in the rat masseter muscle

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Abstract

In this study, we performed a series of experiments to investigate whether substance P (SP) contributes to neurogenic inflammation in the skeletal muscle tissue. Intramuscular injection of an inflammatory irritant, mustard oil (MO), induces significant edema formation in the rat masseter muscle. In order to study the contribution of endogenous SP in the MO-induced edema, groups of rats were pretreated with two different doses (100 nmol; 1 μl) of either peptidergic (Sendide) or non-peptidergic (L703, 606) neurokinin 1 (NK1) receptor antagonist in one masseter muscle 15 min prior to the MO injection in the same muscle. The extent of edema was assessed as the percent weight difference of the injected muscle compared to the non-injected muscle. Neither Sendide nor L703,606 pretreatment resulted in a significant inhibition of the MO-induced edema in the masseter muscle. Exogenous application of SP also produced a significant swelling of the muscle, which was blocked by L703,606 (1 μl) pretreatment, suggesting that evoked release of SP following MO injection is not sufficient to induce significant edema formation. Capsaicin (1% in 25 μl), which is known to cause neurogenic inflammation, failed to produce edema formation in the masseter muscle. The same concentration of capsaicin injected into the hindpaw produced significant swelling of the injected paw. Taken together, these results provide compelling evidence that, unlike cutaneous or joint tissue, SP does not play a critical role in inducing neurogenic inflammation in the skeletal muscle tissue.
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Keywords: Masseter Muscle; Inflammation; SP; NK1 receptor; Mustard Oil; Rat

1. Introduction

Neurogenic inflammation results from the release of bioactive substances from peripheral terminals of small diameter primary afferent neurons via axon reflexes or dorsal root reflexes [10,47]. The inflammation is characterized by vasodilation, edema formation, and hypersensitivity [40], and has been implicated in a variety of inflammatory and pain conditions such as rheumatoid arthritis, migraine headache, chronic pelvic pain, irritable eye syndrome, and bronchial inflammatory diseases [13,24,33,46]. There is now overwhelming evidence that peripheral release of neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP), is largely responsible for neurogenic inflammation [15]. Studies have shown that exogenously administered SP enhances the permeability of synovial blood vessels [44] and increases the severity of joint injury in experimental arthritis in the rat [27]. SP also stimulates early angiogenesis in the knee joint during acute neurogenic inflammation, which has been proposed as a key step in the transition from acute to persistent inflammation [43]. Likewise, the peripheral release of SP induces plasma extravasation in the cutaneous tissue and visceral organs and selective receptor antagonists that block neurokinin receptors significantly reduce the plasma extravasation [2,12,18,25,26,42].

The data on the role of SP in neurogenic inflammation in the skeletal muscle tissue are conflicting. Although the percentage of SP containing muscle afferents is reported to be much higher than those of skin afferents [32,34,37], the level of plasma extravasation following antidromic stimulation of muscle nerve is significantly lower than that

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induced by the stimulation of cutaneous nerve [31]. This may be due to the low level of SP transported from the cell body to peripheral axons of a muscle nerve and plastic changes in peptide expression in primary afferent neurons by some trophic factors in muscle tissue [30]. A recent study in trigeminal ganglia showed that only 5% of primary afferent neurons innervating masticatory muscles stained positive for SP [3], suggesting further differences in the neurochemical profiles of sensory neurons in the trigeminal and spinal systems. However, little information is available on the role of peripheral neuropeptides in mediating craniofacial muscle inflammation and nociception. Since chemical profiles of primary afferent neurons may vary depending on the types of tissue innervated [32,34,36], it is of a significant clinical interest to elucidate the tissue specific mechanisms involved in the development of neurogenic inflammation.

We have previously shown that masseteric injection of small diameter fiber excitant, mustard oil (MO) causes acute inflammation leading to plasma extravasation and edema in the muscle [41]. Since MO is shown to cause neurogenic inflammation in the cutaneous tissue [5,22], it is reasonable to assume that MO-induced edema formation in the masseter muscle is mediated by peripheral release of neuropeptides. In the present study, we conducted a series of experiments to investigate whether SP contributes to neurogenic inflammation in the skeletal muscle tissue by evaluating edema formation in the masseter muscle. Some of these results have been reported in abstract form [8].

2. Materials and methods

2.1. Animal preparation

Experiments were carried out on male Sprague–Dawley rats weighing between 300–400 g. Rats were initially anesthetized with sodium pentobarbital (40–50 mg/kg, i.p.) and maintained by intravenous infusions of pentobarbital (5–7 mg/h). The continuous infusion of pentobarbital was maintained and adjusted to ensure a steady plane of anesthesia. Rectal temperature was monitored and maintained within normal physiological limits for the duration of experiments. All procedures were conducted within the NIH guidelines for Care and Use of Laboratory Animals under a University of Maryland approved IACUC protocol.

2.2. Induction of myositis and edema measurement

Muscle inflammation was induced by injecting a small volume of MO (30 μl, 20% allylisothiocyanate in mineral oil) into the mid-region of one masseter muscle. The injection cannula consisted of a 30-gauge needle connected to PE50 tubing and a Hamilton syringe. MO was manually infused through the injection cannula over 10 s. Following the MO injection, inflammation was allowed to develop for 2 h. Rats were then sacrificed with a lethal dose of sodium pentobarbital followed by transcardiac perfusion with 4% paraformaldehyde in phosphate buffer (pH 7.2). Both inflamed and non-inflamed masseter muscles were dissected out from the lateral surface of the entire zygomatic arch to the lower ends of the mandible. The dissection included both deep and superficial portions of the masseter muscle. As an index of edema formation, we measured the wet weight of both the injected and non-injected masseter muscles and calculated the percent weight difference between the muscles for each animal. We have previously shown that the wet weight of inflamed muscle is 25–30% heavier than the non-inflamed muscle due to the edema formation [42]. In some animals Evans Blue (1%, i.v.) was administered 10 min before the end of the experiment in order to verify inflammation in the muscle, but Evans Blue content was not systematically analyzed in this study.

2.3. Experimental design

The first series of experiments were designed to test the role of SP by antagonizing local NK1 receptors in the muscle in MO-induced edema formation. Two groups of rats (n = 5 each) were treated with different doses of peptidergic NK1 receptor antagonist (Sendide, Neo System, France; 100 nmol; 1 μmol) in one masseter muscle 15 min prior to the MO injection in the same muscle. Since antagonists with a peptide structure are subject to degradation by endogenous peptidases, two separate groups of rats (n = 5 each) received different doses of non-peptidergic NK1 receptor antagonist, L703,606 (RBI, USA; 100 nmol; 1 μmol) in the same manner. An additional group of rats (n = 5) was treated with the same volume of vehicle prior to MO injection.

In the second series of experiments, we examined whether exogenously administered SP can induce edema formation in the muscle. One group of rats (n = 5) was injected with SP (2 μg) in the masseter muscle and edema was measured in the same manner as the MO-injected rats. Another group of rats (n = 5) was pretreated with L703,606 (1 μmol) 15 min before the SP injection.

Finally, since there is a possibility that MO can induce edema via a non-neurogenic component, we injected a group of rats (n = 5) with 1% capsaicin (25 μl), which is known to cause neurogenic inflammation, and evaluated the edema formation in the masseter muscle. The same volume and concentration of capsaicin was also injected into one hindpaw of these rats and the thickness of the injected and non-injected paws were measured and used as control for capsaicin effect.

2.4. Statistical analysis

The weight difference between the injected and non-injected muscles was analyzed using paired t test. Mean percent weight differences were analyzed with either t test or one-way analysis of variance (ANOVA). Post hoc comparison analysis was performed using Dunnett's test.

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