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A Clinically Relevant Animal Model of Temporomandibular Disorder and Irritable Bowel Syndrome Comorbidity

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Abstract: Temporomandibular disorder and irritable bowel syndrome are comorbid functional chronic pain disorders of unknown etiology that are triggered/exacerbated by stress. Here we present baseline phenotypic characterization of a novel animal model to gain insight into the underlying mechanisms that contribute to such comorbid pain conditions. In this model, chronic visceral hypersensitivity, a defining symptom of irritable bowel syndrome, is dependent on 3 factors: estradiol, existing chronic somatic pain, and stress. In ovariectomized rats, estradiol replacement followed by craniofacial muscle injury and stress induced visceral hypersensitivity that persisted for months. Omission of any 1 factor resulted in a transient (1 week) visceral hypersensitivity from stress alone or no hypersensitivity (no inflammation or estradiol). Maintenance of visceral hypersensitivity was estradiol dependent, resolving when estradiol replacement ceased. Referred cutaneous hypersensitivity was concurrent with visceral hypersensitivity. Increased spinal Fos expression suggests induction of central sensitization. These data demonstrate the development and maintenance of visceral hypersensitivity in estradiol-replaced animals following distal somatic injury and stress that mimics some characteristics reported in patients with temporomandibular disorder and comorbid irritable bowel syndrome. This new animal model is a powerful experimental tool that can be employed to gain further mechanistic insight into overlapping pain conditions.

Perspective:* *The majority of patients with temporomandibular disorder report symptoms consistent with irritable bowel syndrome. Stress and female prevalence are common to both conditions. In a new experimental paradigm in ovariectomized rats with estradiol replacement, masseter inflammation followed by stress induces visceral hypersensitivity that persists for months, modeling these comorbid pain conditions.

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Key words: *Comorbid pain, stress, visceral hypersensitivity, irritable bowel syndrome, temporomandibular disorder, estrogen.*

In general, women are more sensitive to pain than men (see[17,22] for review), and a greater number of chronic pain syndromes are more prevalent in women, including irritable bowel syndrome (IBS) and temporomandibular disorder (TMD).[2,11,22,64] Both of these conditions occur largely in premenopausal women, and symptoms fluctuate across the menstrual cycle.[25,29,40,56] Many patients with IBS or TMD report additional pain that is considered unrelated to the primary complaint, resulting in comorbid or overlapping pain syndromes. For example, patients with TMD report symptoms consistent with IBS, chronic pelvic pain, or fibromyalgia.[1,21,67] For several frequently reported chronic pain syndromes, the rate of comorbidity exceeds 50%, making this a significant pain management problem.

Several hypotheses have been put forth to explain these seemingly unrelated comorbid conditions. Psychological factors including stress and/or depression can increase the severity of pain syndromes.[20,26,44] Although acute stress can be antinociceptive, for example, stress-induced analgesia,[8] it often is pronociceptive, especially

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for visceral stimuli.[4,6,12,38] In contrast, chronic stress is typically pronociceptive. It exacerbates acute pain and triggers nociceptive episodes in patients with chronic pain syndromes.[19,23] For example, functional gastrointestinal disorders including IBS are often comorbid with affective disorders such as depression, anxiety, panic, and posttraumatic stress disorder.[10,35,44] Because stress modulates many pain syndromes, it is not surprising that patients susceptible to one chronic pain condition have a high potential for experiencing multiple conditions during/after stressful situations. However, the underlying mechanisms are unknown.

Both hormonal fluctuations and stress modulate nociceptive sensitivity (see[61] for review). As nociceptive stimuli originating in the deep tissues of rodents are especially susceptible to both the changing hormone levels during the estrous cycle and hormone replacement following gonadectomy, animal models can provide useful insight into pain conditions in women. Likewise, animal models of stress have been used to try to gain a mechanistic understanding of functional pain disorders, especially IBS.[39] However, with the exception of diffuse noxious inhibitory controls/conditioned pain modulation, animal models to study the interaction of multiple pain conditions are lacking.

In the present study, we present a new animal model of chronic visceral hypersensitivity that is dependent on 17β-estradiol (E2), prior injury, stress, and the temporal sequencing of these variables. This model mimics the clinical presentation of TMD patients with IBS symptoms, providing a platform to evaluate factors that contribute to these overlapping pain syndromes. Portions of this manuscript have been presented in abstract form.[60]

Methods

Female Sprague Dawley rats (225–250 g) were purchased from Harlan (Indianapolis, IN) and double housed in the University of Maryland School of Dentistry animal facility with a 12-hour light-dark cycle (lights on at 7 AM). Food and water were available ad libitum. All protocols were approved by the University of Maryland School of Medicine Institutional Animal Care and Use Committee and adhered to guidelines for experimental pain in animals published by the International Association for the Study of Pain.

Surgery

Rats were anesthetized with isoflurane and ovariectomized using a dorsolateral approach. Electromyogram (EMG) electrodes made from Teflon-coated 32-gauge stainless steel wire (Cooner Wire Company, Chatsworth, CA) were stitched into the ventrolateral abdominal wall. The electrode leads were tunneled subcutaneously and exteriorized at the back of the neck. Rats were treated pre- and postoperatively with buprenorphine (.03 mg/kg, subcutaneously, twice per day for 2 days). Upon recovery from anesthesia, rats were individually housed for the duration of the study.

Experimental Protocol

The experimental protocol is shown in Fig 1. The objective was to test the effects of prior injury (craniofacial masseter muscle inflammation, a model of TMD), stress (forced swim [FS]), and E2 on visceral and somatic mechanosensitivity. Ten to 14 days following ovariectomy and electrode placement, rats were injected subcutaneously with 50 μg E2 or 100 μL safflower oil (vehicle). The same injection was repeated at 4-day intervals. The bilateral masseter or biceps brachii muscles were injected with complete Freund's adjuvant (CFA, 150 μL, 1:1 in saline) or saline (control for CFA injection). FS stress was produced by placing the rat in a cylindrical container (40 × 50 cm) containing 20-cm-deep water at 26°C for 10 minutes on the first day and 20 minutes on the next 2 days. The control for stress from the FS was to leave the rats undisturbed in their home cage. The day following the last FS was designated day 1. Baseline data were collected prior to the CFA injection/FS and then every 4 to 8 days for 6 weeks post stress. This stress model was chosen because it could be completed between E2 injections or within one 4-day estrous cycle.

Rats were tested for their visceromotor response (VMR) to graded intensities of colorectal distention (CRD), their mechanosensitivity of the lower back (area of referred pain from the colorectum) and forepaw (test for whole body mechanosensitivity) using von Frey filaments, and their threshold to withdrawal from stimulation of the masseter muscle region using an IITC Electronic von Frey anesthesiometer (model no. 2290, tip diameter 4 mm; IITC Life Science Inc, Woodland Hills, CA). The VMR was measured 24 hours following an E2 or oil injection. Mechanosensitivity of the back and forepaw were tested 48 hours following E2 or oil injection, and threshold to orofacial stimulation was tested 72 hours following the injection. Not all rats were tested for somatic mechanosensitivity. There was no difference in the magnitude of the VMR for rats tested for all stimuli (VMR and von Frey on consecutive days) and those tested only for visceral sensitivity, so the VMR data were pooled.

Visceromotor Response

The VMR is the EMG recorded from the abdominal muscles in response to graded intensities of CRD. On the appropriate day as indicated in Fig 1, after the E2 or oil injection, rats were fasted overnight. Water was available ad libitum. The following day, rats were prepared to record the VMR. Rats were briefly sedated with isoflurane and a 5- to 6-cm balloon attached to Tygon tubing (Cole-Parmer, Vernon Hills, IL) was inserted into the descending colon and rectum through the anus. The secured end of the balloon was at least 1 cm proximal to the external anal sphincter, and the tubing was taped to the tail. Rats were loosely restrained in acrylic glass tubes and given 30 minutes to recover from sedation. The EMG signals were recorded with a CED 1401 and analyzed using Spike 2 for Windows software (Cambridge Electronic Design, Cambridge, United Kingdom). CRD was produced by inflating the distention balloon with air. The pressure was monitored and kept

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