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Pain affect in the absence of pain sensation: Evidence of asomaesthesia after somatosensory cortex lesions in the rat

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ABSTRACT

Multidimensional models of pain processing distinguish the sensory, motivational, and affective components of the pain experience. Efforts to understand underlying mechanisms have focused on isolating the roles of specific brain structures, including both limbic and non-limbic cortical areas, in the processing of nociceptive stimuli. The purpose of this study was to examine the role of the somatosensory cortex in both sensory and affective aspects of pain processing. It was hypothesized that animals with lesions of the hind limb area of the somatosensory cortex would demonstrate altered sensory processing (asomaesthesia, a deficit in the ability to detect and identify somatic sensation) in the presence of an inflammatory state when compared to animals with sham lesions. The level of pain affect produced by an inflammatory pain condition was not expected to change, as this region has not demonstrated a role in processing the affective component of pain. Seventy-nine adult female Sprague-Dawley rats were randomly assigned to receive bilateral lesions or a sham procedure. The results showed that somatosensory lesions to the hindlimb region altered responses to mechanical stimulation in the presence of experimentally-induced inflammation, but did not attenuate the inflammation-induced paw volume changes or the level of pain affect, as demonstrated by escape/avoidance behavior in response to mechanical stimulation. Overall, these results support previous evidence suggesting that the somatosensory cortex is primarily involved in the processing the sensory/discriminative aspect of pain, and the current study is the first to demonstrate the presence of pain affect in the absence of somatosensory processing.

1. Introduction

The body of evidence supporting Melzack and Casey's [28] multidimensional model of pain processing has demonstrated considerable support for a dichotomy in the processing of sensory/discriminative and affective/motivational aspects of pain. Sensations that allow an individual to perceive the location, size, and intensity of a noxious stimulus are processed in the lateral pain system, whereas the negative emotional state associated with noxious stimulation is processed by the medial pain system [5–7,13,26,29,30,34,35,37,38,45–47]. Case studies of patients with parietal cortex lesions affecting the somatosensory system have demonstrated the importance of this region for identifying noxious sensations [31,36,41]. An individual with right hemisphere somatosensory cortex (SI and SII) lesions demonstrated a unique clinical condition of asomaesthesia (an inability to detect and identify sensations from the body), in which he was unable to identify the location or intensity of noxious thermal stimulation of the left hand but could still clearly perceive the unpleasantness of the sensation [36]. This suggests that the discrimination of a noxious stimulus is not essential for the perception of pain affect as long as the medial system is intact. A number of animal studies have also examined the role of the somatosensory cortex in various aspects of sensation, including the detection and identification of noxious stimuli, and have provided evidence that the function of the somatosensory cortex in rats is similar to that of humans and higher primates [9,23–25,42].

Studies of pain processing in rodents are inherently encumbered by the difficulty of demonstrating the phenomenon of pain in lower mammals, and behavioral assessments relying on reflexes such as tail flick or paw withdrawal alone can provide only a partial view of the rodent 'pain' experience. Recently, a number

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of paradigms designed to isolate and measure the affective component of nociception in rodents have been developed with this in mind [8,16,27]. The purpose of the current study was to examine the effect of bilateral lesions to the hind paw region of the primary somatosensory cortex (SI) on sensory and affective pain processing in awake, freely moving animals. We assessed sensory thresholds as well as pain affect to determine how the loss of pain sensation might influence the expression of pain affect. Paw withdrawal threshold testing provided a measure of hind paw sensitivity to mechanical stimulation throughout the protocol, to ensure normal functioning before and after stereotaxic surgery as well as quantify the level of hypersensitivity after the injection of complete Freund's adjuvant (CFA) or saline into the left hind paw. Place escape/avoidance paradigm (PEAP) testing [16] occurred only after the injections, and involved a Plexiglas chamber with a dark and light half. Subjects were stimulated with a suprathreshold von Frey every 15 seconds for 30 minutes (on the plantar left paw in the dark, and the right paw in the light). The degree of light side preference was interpreted as an indication of the level of pain affect associated with stimulation of the affected paw, given that subjects treated with saline maintained a preference for the dark side throughout the testing period.

2. Method

2.1. Subjects

A total of 79 adult female Sprague-Dawley rats (n = 10–16 per group) from University of Texas at Arlington vivarium, weighing approximately 200 to 300 g, were used in this study. Animals were housed in groups of 2 to 4 and maintained on a 12:12-hour light/dark cycle with free access to food and water throughout the study. All procedures were approved by the University of Texas at Arlington Institutional Animal Care and Use Committee and were in accordance with the guidelines put forth by the International Association for the Study of Pain [57]. From the original 79 subjects, 7 were eliminated because of inadequate lesion damage.

2.2. Surgical procedures

The organization of the SI region has been studied in detail and the somatotopic map provided by electrophysiology data allowed us to select the hind limb region (SIHL) for our manipulations while limiting the impact of the lesion on normal behavior and sensory processing [9,51,52]. In addition, a nonspecific damage control group was created using bilateral lesions of the barrel cortex (SIBF), a region that has been well studied for its role in processing information from the whisker field and which we determined to be an adequate control for nonspecific lesion effects [33,55].

Stereotaxic surgery was performed using standard procedures. Briefly, animals were anesthetized by intraperitoneal injection of ketamine (100 mg/mL) and xylazine (100 mg/mL) mixed together into a solution (8.25 mL ketamine + 1.75 mL xylazine) that was administered at a volume of .7 ml/kg. Animals were then positioned in a stereotaxic frame with blunt-tipped ear bars and a midline incision was made in the scalp. For animals receiving bilateral lesions, a burr hole was drilled and animals received a 1.5-mA electrical lesion for 10 seconds via a stainless steel insulated wire with no insulation on the tip. For SIHL lesions, the coordinates were ±2.1 mm lateral, −1.5 mm posterior, and −2.1 mm dorsal to bregma at a 0° angle from vertical, whereas SIBF lesions were located at ±5 mm lateral, −1.5 mm posterior, and −3 mm dorsal to bregma [32]. Additional sham-treated animals underwent the same procedure with the exception that no current was passed. Antibacterial solution (10% povidone-iodine solution; Betadine Microbicide) was applied to the surgical site using a cotton-tipped applicator and the incision site was sutured. Depth of anesthesia was monitored by checking for reflexive behaviors (ie., eye blink reflex) and by visually monitoring the rate and depth of respiration. Post-surgical signs of infection or overt signs of discomfort were also closely monitored, and animals were allowed to recover for 7 days before any further experiments were conducted.

2.3. Induction of inflammatory condition

Animals were briefly anesthetized with isoflurane in 100% O_2 (3.5% induction, 3% maintenance). Complete Freund's adjuvant (CFA, 150 μL, mixed 1:1 with normal saline) or normal saline (150 μL) was then injected into the intraplantar surface of the left hind paw and animals were allowed to recover in the home cage. Behavioral testing was delayed for 24 hours following the CFA injection to allow for the inflammatory condition to develop and to eliminate any effects of anesthesia on behavioral outcomes.

2.4. Measurement of tactile allodynia

Animals were placed in a Plexiglas chamber (20 × 10.5 × 40.5 cm) and habituated for 15 minutes. The chamber was positioned on top of a mesh screen so that tactile stimuli could be administered to the plantar surface of both hind paws. Tactile sensitivity for each hind paw was measured using the up/down method [4] with 8 von Frey monofilaments (3.91, 5.91, 9.97, 19.81, 38.82, 78.14, 141.99, and 239.04 mN). Each trial began with a von Frey force of 9.97 mN first delivered to the right hind paw for approximately 1 second, then the left hind paw. The next higher force was delivered if there was no withdrawal response, whereas the next lower force was delivered if there was a response. This procedure was repeated until no response was made at the highest force (239.04 mN) or until 4 stimuli were administered after the initial response. The 50% paw withdrawal threshold for each trial was calculated using the following formula: $[X\text{th}]\log = [vFr]\log + ky$, where $[vFr]$ is the force of the last von Frey used, k = 0.2591 is the average interval (in log units) between the von Frey monofilaments, and y is a value that depends upon the pattern of withdrawal responses [4]. If an animal did not respond to the highest von Frey monofilament (239.04 mN), then y = 1.00 and the 50% mechanical paw withdrawal response for that paw was calculated to be 424.30 mN. Measures of tactile allodynia were performed 3 times and averaged to determine the mean threshold to tactile stimulation (mean paw withdrawal threshold [MPWT]) for the right and left paws for each animal.

2.5. Measurement of edema

To verify the effectiveness of the CFA inflammatory pain model, edema was measured using a plethysmometer (model 7140, Ugo Basile, Italy). This instrument consisted of a reservoir connected to 2 cylindrical Plexiglas chambers that were partially filled with a liquid (prepared fresh each morning prior to testing) consisting of 0.5 g NaCl/L distilled water with 2 mL/L wetting compound added to the solution to ensure that the paw is thoroughly wet (ie, no air bubbles on the skin surface) and does not retain water after dipping. One of the cylindrical chambers was open at the top, whereas the other was closed and contained a sensor to detect and relay real-time changes in water displacement to a device that displayed the magnitude of the change (in mL) on a digital readout. After calibration of the instrument using 1 mL and 2 mL standards, the animals were lightly restrained while the left hind paw was lowered into the open, fluid-filled chamber for the water displacement value to be recorded. The apparatus was then zeroed out, and the procedure was repeated 2 more times for the left hind paw. The