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Pain inhibits pain; human brainstem mechanisms

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ABSTRACT

Conditioned pain modulation is a powerful analgesic mechanism, occurring when a painful stimulus is inhibited by a second painful stimulus delivered at a different body location. Reduced conditioned pain modulation capacity is associated with the development of some chronic pain conditions and the effectiveness of some analgesic medications. Human lesion studies show that the circuitry responsible for conditioned pain modulation lies within the caudal brainstem, although the precise nuclei in humans remain unknown. We employed brain imaging to determine brainstem sites responsible for conditioned pain modulation in 54 healthy individuals. In all subjects, 8 noxious heat stimuli (test stimuli) were applied to the right side of the mouth and brain activity measured using functional magnetic resonance imaging. This paradigm was then repeated. However, following the fourth noxious stimulus, a separate noxious stimulus, consisting of an intramuscular injection of hypertonic saline into the leg, was delivered (conditioning stimulus). During this test and conditioning stimulus period, 23 subjects displayed conditioned pain modulation analgesia whereas 31 subjects did not. An individual's analgesic ability was not influenced by gender, pain intensity levels of the test or conditioning stimuli or by psychological variables such as pain catastrophizing or fear of pain. Brain images were processed using SPM8 and the brainstem isolated using the SUIT toolbox. Significant increases in signal intensity were determined during each test stimulus and compared between subjects that did and did not display CPM analgesia ($p < 0.05$, small volume correction). The expression of analgesia was associated with reduction in signal intensity increases during each test stimulus in the presence of the conditioning stimulus in three brainstem regions: the caudalis subdivision of the spinal trigeminal nucleus, i.e., the primary synapse, the region of the subnucleus reticularis dorsalis and in the dorsolateral pons in the region of the parabrachial nucleus. Furthermore, the magnitudes of these signal reductions in all three brainstem regions were significantly correlated to analgesia magnitude. Defining conditioned pain modulation circuitry provides a framework for the future investigations into the neural mechanisms responsible for the maintenance of persistent pain conditions thought to involve altered analgesic circuitry.
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Introduction

Pain inhibits pain. That is, the intensity of a painful stimulus is reduced by the application of a second painful stimulus. Over recent years, this endogenous analgesic mechanism, known as conditioned pain modulation (CPM) — formerly known as diffuse noxious inhibitory control — has gained considerable attention, primarily due to reports that reduced CPM is associated with increased postoperative pain (Yarnitsky, 2010), the presence of persistent pain conditions (Julien et al., 2005; King et al., 2009; Nahman-Averbuch et al., 2011) and the effectiveness of analgesic medications (Yarnitsky et al., 2012). Furthermore, it is known that CPM is potentially an extremely powerful analgesic mechanism, since in experimental animals it is able to completely inhibit incoming nociceptor signals at the primary synapse (Le Bars et al., 1979).

Despite being a well-described and important phenomenon, the brain circuitry responsible for CPM remains unknown. One significant limitation in defining this circuitry in experimental animals is that to accurately assess CPM one needs to determine the perceived intensity of a painful stimulus prior to and during a second conditioning painful stimulus. Of course, perceived pain intensity cannot be determined in experimental animal preparations but is instead assessed by measuring activity of neurons within the dorsal horn (Le Bars et al., 1979). A difference in perceived pain is then extrapolated from this change in neuronal firing. The few human investigations that have begun to explore the neuronal mechanisms underlying CPM have suggested that the critical circuitry lies within the brainstem since CPM is absent in patients with complete spinal cord transection (Roby-Brami et al., 1987) and in patients with lateral medullary lesions (De Broucker et al., 1990). Experimental animal investigations have shown that activity within the subnucleus reticularis dorsalis (SRD) within the medulla is critical for

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CPM expression (Bouhassira et al., 1992). Furthermore, activity changes in other brainstem regions such as the parabrachial nucleus (PB) and midbrain periaqueductal gray matter (PAG) may also be involved (Bouhassira et al., 1990).

The aim of this investigation was to use human brain imaging to determine sites responsible for CPM in healthy individuals. Given the evidence that CPM critically involves brainstem sites we focused our analysis on the brainstem and hypothesized that CPM analgesia will be associated with signal changes within the SRD, PB and PAG. Applying noxious stimuli to the orofacial region also provided the opportunity to determine changes in neuronal activity at the primary synapse — the caudalis division of the spinal trigeminal nucleus (SpVc). Furthermore, we aimed to determine if all or some of the brainstem CPM circuitry reacts differentially during single noxious stimuli in those individuals that do or do not express CPM analgesia. Once these circuits have been defined we will be in a position to begin to manipulate them in an attempt to provide analgesia in patients with either acute pain or persistent pain.

Materials and methods

Subjects

Fifty-four pain-free subjects (22 males, mean [±SEM] age: 23.1 ± 0.6 years) were recruited for the study. Informed written consent was obtained for all procedures, which were conducted under the approval by local Institutional Human Research Ethics Committees and satisfied the Declaration of Helsinki.

MRI scans

Prior to entering the MRI scanner, a 3 × 3 cm magnetic resonance imaging (MRI) compatible Peltier-element thermode (Medoc) was secured to the skin of the right side of the mouth. To determine a temperature that evoked moderate pain ratings in each individual, the thermode temperature was raised with a Thermal Sensory Analyser (TSA-II, Medoc) from a resting temperature of 32 °C to various temperatures at 0.5 °C intervals between 44 and 49 °C. Temperatures were randomly applied in 15 s intervals for a duration of 10 s, during which each subject continuously rated their pain intensity (0 = no pain, 10 = worse imaginable pain) in real time using a Computerized Visual Analogue Scale (CoVAS, Medoc). The CoVAS is a 10 cm subject-controlled horizontal slider which allows pain intensity to be continuously recorded during the entire fMRI scan on a computer outside the MRI room. The temperature which generated a pain intensity rating of approximately 6 out of 10 was then used for the remainder of the experiment.

Each subject was then positioned supine onto the MRI scanner bed and placed into a 3 T MRI scanner (Intera, Philips Medical Systems, The Netherlands), the head immobilized in a 32-channel head coil to which padding was added to prevent head movement. A fine stainless steel butterfly cannula (23G), connected via a 10 cm tube to a 1 ml syringe filled with sterile hypertonic (5%) saline, was placed ~1 cm into the rostral belly of the tibialis anterior muscle of the right leg. Two series of 140 gradient echo echo-planar image sets with Blood Oxygen Level Dependent (BOLD) contrast were then collected. Each image volume covered the entire brain, extending caudally to include the upper cervical spinal cord (38 axial slices, repetition time = 2500 ms, echo time = 40 ms, field of view = 240 × 240, matrix size = 88 × 84, raw voxel size = 1.5 × 1.5 × 4.0 mm thick; no inter-slice gap). During the first functional MRI (fMRI) series, following a 30-volume baseline period, 8 noxious thermal stimuli (*test stimuli*) were delivered (Fig. 1a). Each noxious stimulus was delivered for 15 s (including ramp up and down periods of 2.5 s each), followed by a 6-volume baseline (32 °C) period. During each period of noxious stimulation, the subject was asked to rate the pain intensity on-line using the CoVAS. During the second fMRI series an identical stimulus paradigm was performed. However, following the fourth noxious stimulus, a bolus injection of 1 ml of hypertonic saline was made into the right tibialis anterior muscle (*conditioning stimulus*) (Fig. 1b). The subject was not informed as to when the noxious stimulus to the leg would be delivered and was instructed to continue to rate the thermal stimulus on the lip and not the stimulus in the leg. A T1-weighted anatomical image was then collected (288 axial slices, repetition time = 5600 ms, echo time = 2.52 ms, field of view = 250 × 174, matrix size = 288 × 288, raw voxel size = 0.87 × 0.87 × 0.87 mm thick).

At the completion of the MRI scanning session, each subject was asked to rate the average pain intensity of the conditioning noxious stimulus, draw the distribution of pain on a standard drawing of the leg and complete a McGill pain questionnaire. To determine the perceived spread of the conditioning stimulus pain, the leg distribution drawing from each subject was placed into ImageJ and the total area of spread determined (number of pixels). Immediately following the MRI session, each subject also completed a pain catastrophizing questionnaire (Sullivan et al., 1995) and the fear of pain questionnaire (Huang et al., 2007). Using the two-standard deviation band method (Nourbakhsh and Ottenbacher, 1994), subjects were placed into either a CPM or noCPM group based on their analgesic response during the second fMRI scan. For each subject, the mean and standard deviation pain intensity ratings of the first four test stimuli were calculated. The means of test stimuli 5 and 6 (during the conditioned pain stimulus period) were then averaged and if this value was more than 2 standard deviations lower than the mean of the first four test stimuli the subject was placed into the CPM group ($n = 23$). The remaining 31 subjects were placed into the noCPM group.

MRI scan analysis

Using SPM8 (Friston et al., 1994) and custom software, fMRI images were realigned and linearly detrended to remove global signal intensity changes. Inspection of the movement parameters derived from the motion correction step revealed that no subject moved more than 1 mm in any direction. As a consequence, all subjects' image sets were used for further analysis. The first 5 volumes were removed due to excess scanner signal saturation. Using the SUIT toolbox in SPM8, the brainstem was isolated and normalized to the SUIT template in Montreal Neurological Institute (MNI) space. To improve signal-to-noise, using custom software we applied a temporally smoothed image sets using a 5 s full-width at half maximum (FWHM) Gaussian filter. Since we were interested in determining signal intensity changes in small brainstem regions, spatial smoothing was not applied.

Significant changes in signal intensity were determined using a repeated box-car model convolved with a canonical hemodynamic response function. To account for subject-to-subject and voxel-to-voxel response variability, we added time and dispersion derivatives, which allow the peak of the signal response to vary by ±1 s and the width of the response to vary, respectively. In each subject, their 6 direction movement parameters (translational: *X*, *Y* and *Z* planes; rotational: tilt, roll and yaw) obtained during the realignment step were included as nuisance variables. In addition, to remove any effects of cerebrospinal fluid movement, signal intensity changes derived from a 2 mm sphere placed in the 4th ventricle were also included as a nuisance variable. Three separate random effects, second level analyses were then performed. Firstly signal intensity changes evoked by the 8 test stimuli applied during the first fMRI scan, were determined in all 54 subjects ($p < 0.05$, false discovery rate corrected for multiple comparisons). Secondly, the effects of CPM on brainstem activity were determined by comparing signal intensity changes during the four test stimuli in the presence of the conditioning stimulus in the CPM and noCPM groups. Thirdly, we determined significant differences in signal intensity between CPM and noCPM subjects during the 8 test stimuli applied during the first fMRI scan. Given we hypothesized that CPM would involve activity changes within the SRD, SpVc and dlPons, we created regions of

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