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RESEARCH ARTICLE

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Temporal summation of pain from skin, muscle and joint following nociceptive ultrasonic stimulation in humans

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Abstract This study investigated the phenomenon of temporal summation in response to repetitive focused ultrasound stimulation of skin, muscle and joint in human volunteers. Stimulation was carried out using a custom-designed, focused ultrasonic stimulator with a resonant frequency of 1.66 MHz. A series of stand-off attachments were used to ensure that the focal region of the ultrasound beam projected either cutaneousely, within the distal interphalangeal joint of the index finger, or within the first dorsal interosseous muscle. Stimulation was carried out using single pulses and trains of five pulses of different pulse durations (25 ms, 50 ms, 75 ms, 100 ms), and using single pulses and trains of five pulses (50 ms duration) at different frequencies (0.5 Hz, 1 Hz, 2 Hz, 3 Hz, 4 Hz, 5 Hz). Tactile perception thresholds, pain thresholds and summation pain thresholds were recorded. Temporal summation of pain could be elicited by stimulation of both skin, joint and muscle, although the influence of temporal summation appeared to be more pronounced for muscle stimulation. Muscle stimulation also required greater ultrasound intensity compared with joint and skin stimulation. Temporal summation could not be elicited by tactile, low-intensity stimulation. Focused ultrasound is a potent, noninvasive technique with which to investigate temporal summation from somatic structures. A number of factors may account for the higher intensities required to elicit pain in muscle and the increased rate of temporal summation. It is clear, however, that if temporal summation is more pronounced in muscle than other tissues then this may be an important factor contributing to pain in musculoskeletal syndromes.

Keywords Muscle pain · Skin pain · Joint pain · Focused ultrasound · Temporal summation

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Introduction

Pain from deep somatic tissue is a major clinical problem and yet the basic mechanisms involved in muscle and joint pain are still not understood. Experimental pain studies with standardised induction and assessment of pain in healthy subjects can give new information on basic mechanisms involved in pain from deep structures (Arendt-Nielsen 1997; Graven-Nielsen et al. 2001). There are a limited number of models that can be used to study muscle pain in humans. Available methods include injection of hypertonic saline or endogenous algesiogenic substances and intramuscular electrical stimulation (Kellgren 1938; Jensen and Norup 1992; Zhang et al. 1993; Arendt-Nielsen et al. 1997; Graven-Nielsen et al. 1997; Rossi and Decchi 1997; Svensson et al. 1997; Babenko et al. 1999; Laursen et al. 1999; Stohler and Kowalski 1999; Witting et al. 2000). The disadvantage of the aforementioned methods is that they involve invasive procedures. An alternative method is stimulation with focused ultrasound, which has been used to induce joint and skin pain (Gavrilov et al. 1977; Tsirulnikov et al. 1986; Wright and Davies 1989; Wright et al. 1993).

The transducer for ultrasound stimulation is located externally but as a result of focusing the beam, the energy can be applied maximally to the deeper tissues, thereby selectively activating nociceptors in deep structures (for reviews, see Davies et al. 1996; Gavrilov et al. 1996). The distance from the ultrasound transducer to the focal region is accurately defined. By appropriate adjustment of this distance, it is possible to focus the main ultrasound energy in the target tissue and thereby use ul-

trasound to stimulate the skin, joints and other subcutaneous structures (Gavrilov 1984; Gavrilov et al. 1977; Tsirulnikov et al. 1986; Wright and Davies 1989; Wright et al. 1993). The diameter of the focal region varies between 6.4 and 1.1 mm for ultrasound transducers, with resonant frequencies between 0.48 and 2.67 MHz (Gavrilov et al. 1977). This suggests that for transducers with a resonant frequency in excess of 1.5 MHz the focal region will be relatively small and facilitate stimulation of specific target tissues. Gavrilov et al. (1977; Gavrilov 1984) report that, while ultrasound may elicit a variety of sensations when used to stimulate skin, stimulation of deeper structures predominantly elicits only a report of pain. As such, ultrasound constitutes a noninvasive means of producing a relatively pure pain sensation in deep tissue structures. However, whether it is possible to induce muscle pain using focused ultrasound stimulation has not been demonstrated explicitly.

The phenomenon that a single nociceptive stimulus by repetition causes exaggerated perceptions of human pain is called temporal summation, which is assumed to be related to the wind-up that can be measured in animal dorsal horn neurons (Arendt-Nielsen et al. 1994; Price et al. 1994; Ren 1994; Arendt-Nielsen and Petersen-Felix 1995). The relationship between temporal summation and wind-up is supported by the finding that both are inhibited by blocking the NMDA receptor (Dickenson and Sullivan 1987; Price et al. 1994; Arendt-Nielsen et al. 1995, 1996; Andersen et al. 1996). Temporal summation has been demonstrated for repetitive electrical and thermal cutaneous stimulation, saline infusion in muscles, electrical stimulation of muscles and electrical stimulation of visceral afferents (Price et al. 1994; Frøbert et al. 1995; Arendt-Nielsen et al. 1997; Graven-Nielsen et al. 1997; Svensson et al. 1997). To date, there has been no study evaluating the temporal summation phenomenon following stimulation of articular or muscle nociceptors by noninvasive techniques.

The aims of the present study were: (1) to assess focused ultrasound as a new noninvasive muscle pain stimulus, (2) to systematically evaluate the effect of stimulus duration on pain perception, and (3) to investigate the phenomenon of temporal summation to repetitive focused ultrasound stimulation of skin, joint and muscle.

Materials and methods

Subjects

The study included 15 healthy subjects (12 men, 3 women) with a mean age of 24 years 6 months (range 21 years 2 months–42 years 9 months). All subjects participated in two separate experiments at least 1 week apart. They were not experiencing any ongoing pain in the hand or arm at the time of the experiment, and subjects with any history of significant pain or surgeries affecting the upper limb were excluded from the study. The subject population did not include any authors of the study and subjects were not informed about the specific hypotheses being tested. Subjects gave their informed written consent prior to inclusion in the study, which had received approval from the local ethics committee and was performed in accordance with the Declaration of Helsinki.

Focused ultrasound stimulation

Ultrasonic stimuli were delivered via a computer-controlled ultrasonic stimulator. This consisted of three main elements: a pulse generator (Philips PM 5138; Germany) externally controlled by a computer, a radio-frequency power amplifier (A300; Electro Navigation Industries, USA) and a focused ultrasonic transducer (Queen's University, Northern Ireland) with a resonant frequency of 1.66 MHz. The function generator produced a 1.66-MHz sine-wave pulse with amplitude, duration and repetition frequency determined by the computer. The power amplifier provided 55-dB amplification of the output signal from the function generator and generated the drive signal that was applied to the ultrasound transducer. Ultrasonic stimuli were delivered as single pulses or trains of five pulses with different durations and interstimulus intervals. Adjusting the amplitude of the sine-wave pulse controlled the intensity of the ultrasonic stimulus. The stimulation intensity could be adjusted in increments of 0.01 arbitrary units (AU) up to a maximum of 1 AU.

The transducer consisted of a circular, concave piezoceramic disc with a diameter of 50 mm. A series of stand-off attachments were used in conjunction with the ultrasound transducer to control the depth to which the focal region of the ultrasound beam penetrated into the tissues tested. The stand-offs were filled with water at room temperature, to provide ultrasonic coupling between the transducer and the subjects' skin. The aperture of each of the stand-offs was the same (15 mm), ensuring that the water surface in contact with the skin was constant for each form of stimulation. By adjusting the stand-off attachments, the distance from the transducer to the focal region of the ultrasound beam was changed and it was possible to project the focal region to the optimal depth within the target tissue. For skin stimulation, the stand-off was adjusted to the upper limit of the focal region, whereas for joint stimulation and muscle stimulation the stand-offs were adjusted such that the focal region projected 5 mm and 7–8 mm below the skin, respectively. Because of the focused nature of the beam, this ensured that maximum ultrasonic intensity occurred within the deep tissues rather than the overlying skin.

Cutaneous stimuli were applied to the skin on the palmar surface of the distal end of the index finger. Articular stimuli were applied to the distal interphalangeal joint of the index finger with the beam being projected from the palmar surface of the finger. Muscular stimuli were delivered to the first dorsal interosseous muscle by projecting the ultrasound beam upwards from the palmar surface of the hand between the first and second metacarpal bones. The focal region of the beam was projected into the central portion of the muscle to avoid stimulating the adjacent metacarpal bones. The metacarpal bones were positioned to either side of the aperture to avoid direct stimulation by the ultrasound beam. At the cutaneous test site, it was possible to induce both tactile and pain sensations depending on the intensity of stimulation. At the other sites the predominant sensation reported was pain. The only extraneous sensation reported by some subjects was that stimulation of the first dorsal interosseous muscle occasionally produced a low-intensity warm sensation on the dorsal skin surface. Minor adjustments were made to finger position to ensure that subjects clearly felt pain in the target tissue and only that location. Subjects were encouraged to keep their hand relaxed and to maintain a constant position during stimulation.

Psychometric parameters

Tactile thresholds, pain thresholds for single stimuli and summation pain thresholds for trains of five stimuli were determined for all subjects. Tactile threshold was determined as the minimum intensity required to obtain a sensation of touch or very light pressure on the skin for both single pulses and pulse trains. Pain threshold was defined as the minimum intensity eliciting pain with a single stimulus pulse. Summation pain threshold was the minimum intensity required to elicit pain at the end of a series of five pulses (Arendt-Nielsen et al. 1994, 1997).