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Reflex receptive fields are enlarged in patients with musculoskeletal low back and neck pain

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ABSTRACT

Pain hypersensitivity has been consistently detected in chronic pain conditions, but the underlying mechanisms are difficult to investigate in humans and thus poorly understood. Patients with endometriosis pain display enlarged reflex receptive fields (RRF), providing a new perspective in the identification of possible mechanisms behind hypersensitivity states in humans. The primary hypothesis of this study was that RRF are enlarged in patients with musculoskeletal pain. Secondary study end points were subjective pain thresholds and nociceptive withdrawal reflex (NWR) thresholds after single and repeated (temporal summation) electrical stimulation. Forty chronic neck pain patients, 40 chronic low back pain patients, and 24 acute low back pain patients were tested. Electrical stimuli were applied to 10 sites on the sole of the foot to quantify the RRF, defined as the area of the foot from where a reflex was evoked. For the secondary end points, electrical stimuli were applied to the cutaneous innervation area of the sural nerve. All patient groups presented enlarged RRF areas compared to pain-free volunteers ($P < .001$). Moreover, they also displayed lower NWR and pain thresholds to single and repeated electrical stimulation ($P < .001$). These results demonstrate that musculoskeletal pain conditions are characterized by enlarged RRF, lowered NWR and pain thresholds, and facilitated temporal summation, most likely caused by widespread spinal hyperexcitability. This study contributes to a better understanding of the mechanisms underlying these pain conditions, and it supports the use of the RRF and NWR as objective biomarkers for pain hypersensitivity in clinical and experimental pain research.

1. Introduction

Pain hypersensitivity is an expression of neuronal plasticity that causes an amplification of the pain sensation, which depends on specific patterns of activation, modulation, or modification of the nociceptive input [46]. It is usually characterized as a state of hyperexcitability of the central nervous system and changes in endogenous pain modulation, resulting in painful perceptions to normally innocuous stimuli (allodynia) or to exaggerated responses to painful stimuli (hyperalgesia). The mechanisms also include facilitated temporal summation and enlargement of the referred pain areas. These alterations are commonly present in chronic musculoskeletal conditions [20], and they are likely relevant from a clinical perspective, as they influence the magnitude of pain and disability [12]. Although pain hypersensitivity has been consistently detected in chronic pain, the underlying mechanisms are difficult to investigate in humans and therefore poorly understood.

The assessment of the underlying central mechanisms behind pain hypersensitivity in humans is a challenging task because direct neural recording is not possible. Instead, a series of psychophysical quantitative sensory tests are usually performed in order to assess a characteristic constellation of sensory signs and symptoms that can be associated with hypersensitivity [34,46]. The rationale behind these tests is that pain hypersensitivity detected after stimulation of healthy tissue has to be a consequence of alterations in central processing [12]. The use of quantitative sensory tests has brought great advancement in the field of pain research; however, they are bounded by inherent limitations, such as their subjective nature, allowing them to be biased, modulated, or influenced by factors not necessarily influencing the central nociceptive processing [43].

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Electrophysiological tests can also be used to assess nociceptive hyperexcitability. In particular, tests based on the nociceptive withdrawal reflex (NWR) and reflex receptive fields (RRF) display some advantages over psychophysical assessments. In the first place, they are objective, in the sense that the outcome of the test does not directly rely on conscious decisions from the researcher/physician or the subject/patient under controlled experimental conditions. They have demonstrated high reliability when performed in healthy volunteers [23,32] as well as in patients with painful conditions [7]. More importantly, they also provide some insight into the location and mechanisms behind the alterations, revealing that at least part of the hypersensitivity is the result of spinal hyperexcitability [14,41]. In relation to this, a recent investigation revealed that patients with endometriosis pain display enlarged RRF [29], thus opening a new perspective in the identification of possible mechanisms underlying hypersensitivity states in humans.

The primary aim of the present study was to test the hypothesis that RRF are enlarged in patients with acute and chronic musculoskeletal pain conditions compared to healthy volunteers. Additionally, NWR and pain thresholds after single and repeated electrical stimulation of the sural nerve were analyzed in order to test subjective pain sensitivity, facilitated temporal summation, and spinal excitability. The results were expected to provide insights into the mechanisms underlying chronic musculoskeletal pain and to offer a perspective to identify potential biomarkers for the objective assessment of central hyperexcitability in humans.

2. Materials and methods

2.1. Participants

2.1.1. Patients

Patients were recruited at the Department of Anaesthesiology and Pain Therapy of the University Hospital of Bern, Inselspital. Forty patients with chronic neck pain, 40 patients with chronic low back pain, and 24 patients with acute low back pain participated in the study. The patients with chronic low back pain were part of a case-control study that was recently published [27]. Inclusion criteria for chronic pain patients were daily pain of at least 6 months' duration and pain at the time of testing with an intensity of at least 3 on a 10-cm visual analog scale, with 0 indicating no pain and 10 the worst pain imaginable. Inclusion criteria for acute pain patients were daily pain for no longer than 4 weeks, no history of chronic low back pain, and pain at the time of testing with an intensity of at least 3 on a 10-cm visual analog scale, with 0 indicating no pain and 10 the worst pain imaginable. Exclusion criteria were radicular pain (as defined by leg pain associated with a magnetic resonance imaging finding of herniated disc or foraminal stenosis with contact to a nerve root), peripheral or central neurological disorders, diabetes mellitus, insufficient knowledge of the German language, pregnancy (as excluded by a pregnancy test), breast-feeding, intake of oral contraceptives or hormones, intake of opioids and antidepressants during the previous 2 weeks, and intake of other analgesics during the 48 h before testing. All subjects provided written informed consent before participating. The study protocol was approved by the local ethics committee of the Canton of Bern, and the study was performed in accordance with the Declaration of Helsinki.

2.1.2. Pain-free subjects

The control group consisted of 300 pain-free subjects who had been recently analyzed to determine the reference values of the reflex parameters in the pain-free population [25]. Exclusion criteria were the same as for the patient group, plus the following: any pain at the time of testing or history of chronic pain syndrome of any nature.

2.2. Descriptive variables

To provide comprehensive information about the patient population, several descriptive variables were recorded, including gender, age, height, weight, and body mass index, pain intensity at the time of testing, and maximum pain intensity ever experienced. Volunteers were also asked to complete the following questionnaires: Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), and Catastrophizing Scale of the Coping Strategies Questionnaire (CSQ). A thorough description of the questionnaires is provided by Neziri et al. [29].

2.3. Electrophysiological and psychophysical pain tests

The main end point according to the study hypothesis was the assessment of RRF. Secondary end points were subjective pain thresholds and parameters of spinal cord nociceptive excitability, namely NWR thresholds to single and repeated electrical stimulation. All the experiments were performed by the same investigator (AN). During the testing session, the volunteers were lying in a bed in a quiet room. A leg rest was placed under the knee to obtain a 10° flexion. Each subject underwent a training session for all tests in order to get familiar with the stimulation procedures before starting the data collection. Tests for RRF, single electrical stimulation, and repeated electrical stimulation were performed in a randomized order. All the tests were applied to the same body side within each subject, with the side being selected randomly by the investigator in a ratio of 1:1.

2.3.1. RRF assessment

[26] have previously described a detailed procedure to assess the RRF. In short, 10 surface electrodes (15 × 15 mm, type 700, Ambu A/S, Denmark) were mounted on the sole of the foot, and a common anode (50 × 90 mm electrode, type Synapse, Ambu A/S, Denmark) was placed on the dorsum of the foot. Each stimulus consisted of a constant current pulse train of 5 individual 1-ms pulses delivered at 200 Hz (Stimulator Noxitest IES 230, Aalborg University, Denmark), felt as a single stimulus. The current intensity was increased from 1 mA in steps of 0.5 mA as the pain sensation was evoked (pain threshold) for each of the 10 stimulation sites. To avoid the subjects' gradual adaptation to the stimulus while determining the pain thresholds at the different sites, the identified pain threshold at the arch of the foot was repeatedly presented to the volunteer for reference. After all pain thresholds were determined, a stimulus with an intensity equal to that 1.5 times higher than the individual pain threshold was delivered 4 times to each individual site, for a total of 40 stimulations. A computer-controlled electrical relay delivered the stimulus to 1 of the 10 electrodes in a randomized sequence at random time intervals (between 8 and 12 s), so that the subject was not aware of when the stimulus was applied. The NWR was measured by surface electromyographic (EMG) electrodes (type 720, Ambu A/S, Denmark) over the belly of the tibialis anterior muscle (interelectrode distance of 2 cm) because the expected biomechanical response to stimulation of the sole of the foot is primarily ankle dorsiflexion [2]. The EMG signals were amplified (up to 50,000 times), filtered (5–500 Hz, second order), sampled (2000 Hz), displayed on the computer screen, and stored on a computer disk. The EMG signals were recorded from 200 ms before stimulation until 1000 ms after stimulation onset. EMG reflex responses were quantified using root–mean–square (RMS) amplitude in the 60–180-ms poststimulation