Clinical Neurophysiology 125 (2014) 352–362

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Central sensitization in spinal cord injured humans assessed by reflex receptive fields

José Alberto Biurrun Manresa [a,*], Nanna Susanne Brix Finnerup [b], Inger Lauge Johannesen [c], Fin Biering-Sørensen [d], Troels Staehelin Jensen [b], Lars Arendt-Nielsen [a], Ole Kæseler Andersen [a]

[a] Center for Sensory-Motor Interaction, Aalborg University, Denmark
[b] Danish Pain Research Center, Aarhus University Hospital, Denmark
[c] The Spinal Cord Unit, Viborg Hospital, Viborg, Denmark
[d] Clinic for Spinal Cord Injuries, The Neuroscience Centre, Rigshospitalet and Faculty of Health Sciences, University of Copenhagen, Denmark

ARTICLE INFO

Article history:
Accepted 30 June 2013
Available online 22 July 2013

Keywords:
Central sensitization
Nociceptive withdrawal reflex
Reflex receptive fields
Descending control
Spinal cord injury
Capsaicin

HIGHLIGHTS

- People with spinal cord injury can develop central sensitization, despite lacking supraspinal input and altered spinal/supraspinal processing.
- Reflex receptive fields are significantly larger and display a distinct different topography in spinal cord injured volunteers compared to non-injured volunteers.
- Protective plastic mechanisms may still be functional in people with spinal cord injury.

ABSTRACT

Objective: To investigate the effects of central sensitization, elicited by intramuscular injection of capsaicin, by comparing the reflex receptive fields (RRF) of spinally-intact volunteers and spinal cord injured volunteers that present presensitized spinal nociceptive mechanisms.
Methods: Fifteen volunteers with complete spinal cord injury (SCI) and fourteen non-injured (NI) volunteers participated in the experiment. Repeated electrical stimulation was applied on eight sites on the foot sole to elicit the nociceptive withdrawal reflex (NWR). RRF were assessed before, 1 min after and 60 min after an intramuscular injection of capsaicin in the foot sole in order to induce central sensitization.
Results: Both groups presented RRF expansion and lowered NWR thresholds immediately after capsaicin injection, reflected by the enlargement of RRF sensitivity areas and RRF probability areas. Moreover, the topography of the RRF sensitivity and probability areas were significantly different in SCI volunteers compared to NI volunteers in terms of size and shape.
Conclusions: SCI volunteers can develop central sensitization, despite adaptive/maladaptive changes in synaptic plasticity and lack of supraspinal control.
Significance: Protective plastic mechanisms may still be functional in SCI volunteers.

1. Introduction

Most of the forms of synaptic plasticity that occur in the spinal cord in response to noxious stimuli, such as post-injury pain hypersensitivity (Woolf, 1983) and spinal long-term potentiation (Woolf and Salter, 2000), can be enclosed into the term *central sensitization* (Ji et al., 2003). Several types of experimental nociceptive activation can induce central sensitization; commonly used human sensitization models involve chemical irritation (e.g. capsaicin) or electrical stimulation of the skin (Simone et al., 1989; Treede et al., 1992; Magerl et al., 1998; Koppert et al., 2001; Klein et al., 2004; Geber et al., 2007). These surrogate models are commonly used in healthy volunteers to study the underlying mechanisms associated with central sensitization, aiming to extrapolate the findings to those cases where sensitization is present as part of pathophysiological pain disorders (Woolf, 2011).

These models, however, have not been extensively studied in cases when there already exists a clinical condition that affects

* Corresponding author. Address: Center for Sensory-Motor Interaction, Department of Health Science & Technology, Aalborg University, Fredrik Bajers vej 7, 9220 Aalborg, Denmark. Tel.: +45 9940 8715; fax: +45 9815 4008.
E-mail address: jbiurrun@hst.aau.dk (J.A. Biurrun Manresa).

1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2013.06.186

the central nervous system. In particular, people with complete spinal cord injury (SCI) already present signs of sensitization, such as nociceptive reflex hyperexcitability and enlarged receptive fields (Andersen et al., 2004), so it is crucial to determine if the protective plastic mechanisms triggered after intense nociceptive activation are still functional (Latremoliere and Woolf, 2009). From a clinical perspective, although several maladaptive changes to sensory processing may contribute to the development of neuropathic pain in SCI patients, there is significant evidence indicating that central sensitization plays a prominent role (Tan and Waxman, 2012). Therefore, this reinforces the importance of the investigating the central mechanisms of pain in order to assess their suitability as targets for treatment (Woolf, 2011).

Furthermore, a critical issue associated with spinal cord injuries is the partial or total loss of supraspinal control. Most of the early studies on supraspinal control mainly focused on descending inhibition, although it was later established that both inhibitory and facilitatory descending control mechanisms are involved in nociceptive modulation (Fields et al., 2006; Heinricher et al., 2009; Ossipov et al., 2010). In this regard, there is increasing evidence of a significant contribution of supraspinal influences to the development and maintenance of central sensitization (Urban and Gebhart, 1999; Sandkühler, 2009). Thus, it is highly relevant to investigate if central sensitization models can still be established in the presence of adaptive/maladaptive changes in synaptic plasticity and complete lack of supraspinal input.

Central sensitization is often assessed using psychophysical measures (Raja et al., 1999; Klein et al., 2005), but these methods are subjective and cannot be applied in people that suffered complete sensory loss after SCI. However, it has been documented that central sensitization can be objectively assessed in humans by the nociceptive withdrawal reflex (NWR) (Biurrun Manresa et al., 2010b; Lim et al., 2011) and the reflex receptive fields (RRF) (Neziri et al., 2010b). Variations in the NWR and the RRF are likely to reflect changes in central processing of nociceptive activity, for instance after repetitive painful stimulation leading to temporal summation (Gozariu et al., 1997; Andersen et al., 2005), or increased excitability in clinical conditions (Banic et al., 2004; Neziri et al., 2010b; Lim et al., 2011). Moreover, descending modulation affects the RRF control following strong nociceptive input, since the responses through the reflex pathways are facilitated by central sensitization and this phenomenon depends on the site of injury and the degree of supraspinal control (Harris and Clarke, 2003).

The aim of the present study was to investigate the effects of central sensitization, as elicited by intramuscular injection of capsaicin, in the presence of altered spinal/supraspinal nociceptive processing. Responses of volunteers with complete SCI and spinally-intact volunteers were objectively assessed and compared using the NWR and the RRF. Finally, a model describing the changes of the functional organization of the nociceptive reflex pathways during central sensitization is proposed and discussed.

2. Materials and methods

2.1. Volunteers

Fifteen volunteers with clinically complete spinal cord injury (15 males, mean age 43 years, range 27–66, see Table 1 for details), classified as grade A according to the American Spinal Injury Association (ASIA) impairment scale (AIS) (Marino et al., 2003) with injuries between T6 and T12 to minimize the risk of autonomic dysreflexia (Helkowski et al., 2003) and fourteen spinally-intact, healthy volunteers (12 males and 2 females, mean age 23 years, range 19–28) participated in the experiment. These groups will be referred to as SCI (spinal cord injured) and NI (non-injured), respectively. Written informed consent was obtained from all volunteers prior to participation and the Declaration of Helsinki was respected. The study was approved by the local ethical committee of the North Denmark Region, Denmark (approval no. VN20060029MCH).

2.2. Setup

2.2.1. Electrical stimulation

Eight surface stimulation electrodes (15 × 15 mm, type Neuroline 700, Ambu A/S, Denmark) were mounted in a non-uniform grid on the plantar side of the right foot. Fig. 1 shows the spatial location of the stimulation electrodes, numbered from 1 to 8. One large common anode (70 × 100 mm, type Pals Platinum, Axelgaard Ltd., USA) placed on the dorsum of the foot ensured that the stimulus was perceived as coming from the sole of the foot. Thick epidermal layers on the sole of the foot of NI volunteers were ground off in order to reduce the effects of variation in skin thickness. Each train of pulses consisted of a 5 square-wave pulses of 1 ms width delivered at 200 Hz, generated by a computer-controlled constant-current stimulator (Noxitest IES 230, Aalborg, Denmark). The stimulation consisted of a burst of 8 trains of pulses delivered at 3 Hz, in order to elicit temporal summation (Arendt-Nielsen et al., 2000). In order to set the stimulation intensity, the NWR threshold had to be determined first. The NWR threshold was defined as the stimulation intensity that elicited EMG activity in the tibialis anterior muscle with an amplitude exceeding 20 μV for at least 5 ms in the 60–180 ms post-stimulation interval after a single stimulus in NI volunteers (Neziri et al., 2010a). In SCI volunteers, the quantification interval was extended to 250 ms after stimulation (Andersen et al., 2004). The final stimulation intensity was set as 0.8 times the average NWR threshold over sites 2, 4 and 6. This stimulation intensity was fixed for the rest of the experiment. The stimuli were delivered using a computer-controlled electrical relay, which consists of opto-electrical switches that sustain high voltages and hence provide extra security in the stimulator system. All relays were closed except in the short period when the stimulus was delivered, in which only the selected stimulation channel was opened (Biurrun Manresa et al., 2010a). All sites were stimulated 4 times in a randomized sequence for each condition (see Section 2.2.4 for details on the conditions), and the program delivered the stimuli at random time intervals so that the volunteers were not aware of when or where the stimulus was applied. The inter-stimulus interval ranged from 10 to 15 s for NI volunteers and at least 30 s for SCI volunteers in order to minimize habituation. Each assessment (i.e., 4 stimulations to each of the 10 sites) took between 15 and 25 min.

2.2.2. EMG recordings

Activity in the tibialis anterior muscle was measured using surface EMG. Initially the skin was lightly abraded, and then two surface electrodes (30 × 22 mm, type Neuroline 720, Ambu A/S, Denmark) were placed along the muscle fiber direction over the muscle with an inter-electrode distance of 20 mm. The signal was amplified (up to 20,000 times), filtered (5–500 Hz, 2nd order), sampled (2000 Hz) and stored (3000 ms window including 200 ms of pre-stimulation activity). Fig. 1 shows example traces of EMG from SCI and NI volunteers.

2.2.3. Capsaicin injection

A solution of 10 μg of capsaicin in 0.1 ml volume was injected into the flexor digitorum brevis muscle (flexor of the toes) in the central compartment of the foot. The tip of the needle was carefully wiped before the injection, to avoid leakage of capsaicin to the skin. None of the volunteers reported pain in the interval between