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Research Report

An experimental model to measure excitatory and inhibitory pain mechanisms in humans

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ARTICLE INFO

Article history:
Accepted 25 June 2008
Available online 9 July 2008

Keywords:
Pain perception
DNIC
Temporal summation
Heat pain
Sex difference

ABSTRACT

Numerous approaches have been used to induce and measure experimental pain perception with the goal of better understanding excitatory and inhibitory pain mechanisms. In this study, the objective was to develop a simple experimental design which would enable us to elicit and measure multiple nociceptive mechanisms that have been reported to play a role in the development and persistency of chronic pain, such as temporal summation (TS) and diffuse noxious inhibitory control (DNIC). Eighty-three healthy subjects (42 men, 41 women) participated in this study where we examined pain perception of two tonic heat pain stimulation (thermode) separated by a 2 minute cold pressor test (CPT) (7 °C, 10 °C or 12 °C) which allowed us to activate DNIC. The heat pain response was characterized by a peak pain during the first 30 s, which was stronger for women ($p=0.001$). We also observed a TS phenomenon during the second minute of stimulation. DNIC's analgesia was assessed by measuring the difference in pain ratings between the two thermode procedures, before and after inducing DNIC by a cold pressure test on the opposite arm. We found that the mean pain ratings and peak pain but not TS were significantly reduced by DNIC. No sex differences were observed in DNIC analgesia. Our experimental pain design allowed us to measure several excitatory and inhibitory pain mechanisms in one experimental session. We were able to separate the effect of DNIC on the peak pain and on TS. This method is simple, sensitive and can easily be used in different population of either healthy subjects or chronic pain patients.

1. Introduction

In experimental pain research, several approaches have been used to induce and measure pain perception. The main reason to use experimental pain in healthy subjects and in patients is to obtain a better understanding of the excitatory and inhibitory mechanisms operating in different conditions. Outcomes such as pain threshold (PTh), pain tolerance (PTol) and mean pain perception are indicators of one's interpretation of nociceptive inputs. Different pain modalities (thermal, electrical, chemical), and also different stimuli duration (phasic, repetition at high or low frequency, tonic) are currently used to induce experimental pain. Experimental pain also allows us to safely mimic a clinical situation in healthy subjects or patients in order to verify their reaction to a nociceptive stimulation or an analgesic procedure. Of all the

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0006-8993/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2008.06.120

different methods, the tonic pain model has been thought to better mimic clinical pain (Rainville et al., 1992). Furthermore, the tonic pain model allows us to measure a greater number of variables related to nociception, such as temporal summation (TS) (Price and Dubner, 1977; Granot et al., 2006) and the effectiveness of endogenous pain control mechanisms (previously measured using a spatial summation model (Marchand and Arsenault, 2002) and a temporal summation model (Potvin et al., 2007).

Pain is a dynamic phenomenon under the influence of several excitatory and inhibitory endogenous pain control mechanisms. Excitatory mechanisms such as TS and central sensitization, associated with repetitive (Price and Dubner, 1977) or persistent stimulations (Granot et al., 2006) are critically involved in the development of chronic pain. Studying TS will help to better understand the mechanisms of central sensitization in humans and its potential role in the development and persistency of certain chronic pain conditions. Pain inhibitory mechanism, such as diffuse noxious inhibitory controls (DNIC), originally described by LeBars et al. (1979), is of particular interest since a deficit of this mechanism is associated with the development of chronic pain (Edwards, 2005). For example, a deficit of endogenous pain inhibition was found to play an important role in some chronic pain conditions like fibromyalgia (Julien et al., 2005; Kosek, and Hansson, 1997; Lautenbacher, and Rollman, 1997). This central pain control mechanism is triggered by persistent nociceptive afferents from nociceptive fibres (A-delta and C-fibres). Once activated, it inhibits nociceptive activity arising from the afferent primary fibres at multiple levels of the dorsal horn, resulting in diffuse pain inhibition. These descending pain pathways originate from the brainstem and have significant inhibitory actions on nociceptive activity, and thus, pain perception (LeBars et al., 1992). This form of analgesia is also known as counter-irritation induced analgesia.

DNIC analgesia is typically quantified by calculating the difference in pain ratings given before and after a painful conditioning stimulus; since the conditioning stimulus activates DNIC, pain perception following this conditioning stimulus should be lower than before the conditioning stimulus (Talbot et al., 1987; Edwards et al., 2003; Serrao et al., 2004; Ge et al., 2004; 2005; Goffaux et al., 2007). We previously developed a spatial summation paradigm to measure the effect of excitatory and inhibitory mechanisms in a single test (Marchand and Arsenault, 2002) and were able to demonstrate that the inhibitory component of the test was opioidergic (Julien, and Marchand, 2006). Other methods have been used, such as repetitive phasic pain (TS paradigm) (Edwards, and Fillingim, 2001; Sarlani and Greenspan, 2002). However, this method might be less sensitive than others since it failed to show the inhibitory effects of DNIC in healthy women (Staud et al., 2003). Recently, it was found that constant nociceptive stimulation (which is more relevant to clinical pain) yields comparable results to the classical repetitive phasic TS procedure (Granot et al., 2006). Finally, even if abundant literature has been published concerning DNIC, there is no agreement concerning the best and most reliable way to quantify the analgesic effect of the DNIC which is of great importance in pain research.

Considering the potential role of endogenous excitatory mechanisms such as TS and endogenous pain control mechanisms in the development and persistence of some chronic pain conditions, it is important to use experimental pain models that can give us as much information as possible on these mechanisms both in healthy subjects and also with different chronic pain populations. We previously used a spatial summation model to measure the interaction between excitatory and inhibitory mechanisms in healthy subjects (Marchand and Arsenault, 2002) and in patients (Julien et al., 2005). The spatial summation procedure consisted of two sessions, on two different days. Only few studies reported experimental protocols permitting to measure both excitatory and inhibitory pain mechanism in one relatively brief session (45 min) (Staud et al., 2003; Granot et al., 2008). Our protocol has the advantage of measuring temporal summation and DNIC using a tonic painful stimulus, which more closely mimics clinical pain (Rainville et al., 1992).

Therefore, the main objective of this study was to develop and test a relatively simple experimental design which would enable us to elicit and/or measure multiple nociceptive and analgesic mechanisms, such as TS, tonic pain perception, and the effect of DNIC in a single session.

2. Results

2.1. *Participants*

After approval from the hospital review board, we collected data from 83 healthy volunteers, 42 men and 41 women (see Table 1). None of the participants was suffering from any known diseases and none was taking medications. The entire experimental procedure lasted about 60 min. The experiment took place at the Clinical Research Centre of the Sherbrooke University Hospital, Sherbrooke, Quebec, Canada. Subjects were recruited through local ads and were all French speaking community-dwelling individuals. All participants gave their written informed consent for their participation in the study.

2.2. *Tonic experimental heat pain before immersion*

The average response curve acquired during the tonic heat pain test for all subjects is presented in Fig. 1a. During the first part of this tonic pain test the thermode temperature

Table 1 – Participants characteristics

Subject's characteristics	Men	Women	All subjects	*p*-value (α=0.05)
Age (y.o.)	22.7 (3.1)	22.8 (2.8)	22.8 (2.9)	NS
Pain threshold (°C)	43.7 (3.3)	41.5 (3.3)	42.6 (3.6)	NS
# Subject/group (*n*)				
CPT 7 °C	14	13	27	NS
CPT 10 °C	14	14	28	NS
CPT 12 °C	14	14	28	NS
Total	42	41	83	NS