SINGLE PULSE VERSUS PULSE TRAIN CUTANEOUS ELECTRICAL STIMULATION DURING COLD PRESSOR TEST

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Abstract

In the present study the effect of the cold pressor test (CPT) on the processing of electrical single pulses (SP) with changing amplitude and pulse trains (PT) with fixed amplitude was analysed using subjective pain ratings and evoked potentials.
Healthy subjects were electrically stimulated at the left middle fingertip in a CPT and control protocol. In the CPT protocol the hand was immersed in water of 0-1°C; in the control protocol in water of 32°C. A total of 105 stimuli were applied in a protocol of five different stimulus amplitudes or number of pulses (NoP). The results showed a decrease of amplitude of EP wave components and decrease of subjective ratings by CPT, for both SP and PT. The relationship between NRS or EP amplitude and stimulus amplitude (SP) or NoP (PT) was unchanged by CPT.

1 Introduction

At present our knowledge of various processes involved in chronification of pain is limited. Novel observation techniques can contribute to increase our understanding of neurophysiological mechanisms in pain processing.
Earlier, we used evoked potentials (EPs) to measure cortical activations reflecting central processing of pain. For an adequate interpretation of EPs well defined stimuli are required. Changing the stimulus strength might give further insight in the sensitivity of central pain mechanisms. In a previous study [5] a comparison between single pulse (SP) and pulse train (PT) electrocutaneous stimulation was performed. In the SP method the amplitude of a single pulse is changed, while in the PT method the number of (fixed amplitude) pulses (NoP) in a train is varied. Nociceptive and sensory nerve fibers in the skin are activated in different proportions by both methods. Changing the stimulus amplitude by SP results in a change in the proportion of both types depending on local fiber densities. Increasing the NoP results in a repeatedly activation of an unchanged proportion of fibers. We showed that both SP and PT influence subjective ratings and evoked potentials (EP) components differently. A linear relationship was obtained using SP, while use of PT showed a curved effect [5].
In this study we use an additional modulating pain stimulus. This might give further insight in the differences in processing by SP and PT. A commonly used modulating stimulus is the cold pressor test (CPT). Several studies show a decrease in pain thresholds by the CPT. Furthermore, also subjective pain ratings and EP amplitudes for laser stimulation show a decrease by CPT [6]. Inhibition of pain thresholds, subjective pain ratings and EP components by CPT in healthy persons is ascribed to diffuse noxious inhibitory control (DNIC) [3]. DNIC is a phenomenon whereby activity of convergent neurons (wide dynamic range neurons) in the dorsal horn is inhibited by stimulation of nociceptive fibers in an area in the body distal from their excitatory receptive field [3]. In literature, pain patients showed impairment of DNIC [2, 7]. In patients with fibromyalgia a modulating stimulus did not cause modulation of pressure pain [2]. But on the other hand, irritable bowel syndrome patients showed hypersensensitivity to pain stimuli by a modulating stimulus [7].
In this study we analysed the effect of the CPT on the processing of SP and PT stimuli in healthy subjects using subjective pain ratings and EP components.

2 Methods

2.1 Subjects

Ten male and eight female right-handed, healthy subjects (age 41,0 ± 14,3) participated in the study. All subjects gave their written informed consent according to the Declaration of Helsinki. The study was approved by the ethical committee of the Medisch Spectrum Twente, Enschede.

2.2 Electrical stimulation

The subjects were electrically stimulated at the left middle fingertip. Stimulation at the fingertip corresponds to the IES method [1]. An electrode with a 1 mm diameter tip of gold in an insulating material was used. A small opening was drilled in the upper layer of the skin of the fingertip using a dental gimlet with the same diameter as the tip of the stimulation electrode [1]. If the sensation threshold was higher

than 1 mA the preparation was regarded insufficiently and tried again. A rectangular surface electrode (a 4x9cm Klinerva Blue Electrode) was placed at the upper part of the left forearm as an anode. The stimulus was a current bipolar rectangular pulse with a stimulus duration of 0.2 ms. Such a stimulus produces a clear pinprick sensation. The electrode was placed in a way that all subjects reported a mild prickling sensation at sensation threshold.

2.3 Sensation and pain threshold

For each subject, the stimulus amplitudes corresponding to the subjective sensation threshold (I_S=0.3±0.22mA) and pain threshold (I_P=1.47±0.63) were determined once before the first protocol. Thresholds were obtained by the ascending method of limits by increasing the stimulus amplitude with steps of 0.1 mA starting at a level of zero.

2.4 SP method

For SP, the stimulus amplitude of a single pulse was varied depending on the obtained I_S and I_P (see equation below).

$$I = I_P - q \cdot (I_P - I_S) \quad q= -0.5, -0.25, 0, 0.25, 0.5 \quad (1)$$

In anticipation of habituation effects [4], the minimum stimulus amplitude was set in between sensation and pain threshold. Decreasing the amplitude further below this minimum stimulus amplitude would probably result in large numbers of unperceived stimuli.

2.5 PT method

The fixed stimulation current for PT was chosen similar to the minimum stimulus amplitude $I_{-50\%}$ of SP (equation 1, q=-0.5). Since we used an IES electrode, selective stimulation of nociceptive afferents (Aδ-fibers) alone is probably not possible. In order to activate Aδ-fibers as selective as possible we therefore chose the minimum stimulus amplitude of SP as stimulus amplitude of PT.

The NoP for PT varied from 1, 3, 5, 7, to 9 pulses. The inter-pulse interval (IPI) between two subsequent pulses in the pulse train was 5 ms. With 5 ms IPI, i.e. well outside the refractory period, fibers have enough time to regenerate. To make sure that stimulation by PT was tolerable, the five NoP were applied in increasing order before the protocol. Although the stimulus amplitude of PT was below the subjective pain threshold, subjects described stimulation by a train of five pulses as a clear prickling painful sensation.

2.6 CPT or control protocol

A polystyrene squared vessel was filled with ice water 0-1°C (CPT) or 32±0.5°C (control). The right hand was immersed up to the wrist in the water. During CPT the subjects were stimulated to keep their hand in the water as long as possible with a maximum of three minutes. After three minutes subjects were asked to withdraw the hand. After 1 minute subjects had to re-immerse the hand. This procedure was continued until the end of the session (about 9.5 minutes). Time to hand withdrawal and re-immersion was recorded. Pain intensity and unpleasantness increases rapidly and peaks in the first 20-40 seconds (Arendt-Nielsen 1992, Talbot 1987). Therefore, electrical stimuli at the left fingertip were applied 30 seconds after hand immersion.

2.7 EEG recordings

Electrical brain activity was continuously recorded using 64-channel EEG. AgCl electrodes were placed according to the extended international 10-20 system. The scalp electrode impedance was less than 5kΩ. An electrode was placed above and under the left eye for electrooculogram (EOG) recording. Data recorded at C_Z referred to linked earlobes (A_1A_2) were analysed. The EEG was recorded at a sample frequency of 5 kHz and re-sampled offline to 1 kHz. The signals were filtered offline at band-pass 0.3-120 Hz. Data up to 100ms pre-stimulus was used for baseline correction. The time window of analysis was 100 ms pre-stimulus and 400 ms post-stimulus.

2.8 Numeric rating scale

Subjects were asked to rate orally the perceived strength of each electrical stimulus on an 11 point NRS. Zero corresponded to “no sensation” whereas 10 corresponded to “strongest imaginable pain”. The first stimulus corresponded for SP with the pain threshold $I_{0\%}$ (equation 1, q=0) and for PT with a train of 5 pulses at $I_{-50\%}$ (equation 1, q=-0.5). The subjects were instructed to rate the first stimulus with a six. Furthermore, after the CPT subjects were asked to rate orally the perceived strength of the right hand on the similar NRS scale.

2.9 Procedure

The experiment consisted of two blocks of three protocols; a block for both SP and PT. A block consisted of a baseline, CPT and a control protocol.

The order of the blocks and the order CPT and control protocol were randomized.
During the baseline protocol a total of 100 identical electrical stimuli were applied at the left middle fingertip. For SP the stimulus was a single pulse at pain threshold (q=0) and for PT 5 pulses at minimum stimulus amplitude (q=-0.5). Data of the baseline measurements will not be discussed here.
During the CPT and control protocol a total of 105 electrical stimuli were applied with 21 stimuli for each of the five stimulus amplitudes (SP) or five NoP in a pulse train (PT). The inter stimulus interval between two successive stimuli was randomly varied between 4 and 6 seconds.
The inhibitory effect of the CPT can persist for several minutes even after withdrawal of the hand. Therefore, to be sure that there was no effect of CPT in a subsequent protocol we waited 15 minutes between the CPT and the control protocol and between the two blocks.

Table 1: Experimental set-up. The experiment consists of two blocks of three protocols with SP or PT stimulation. Order of blocks SP or PT is randomized. A block consisted of a baseline, control and CPT protocol. The order of control and CPT is randomized. Between control and CPT and two blocks there was a break of 15 minutes.

Stimulation method	SP[1]					PT[1]			
protocol	Baseline	Control[2]	Break	CPT[2]	Break	Baseline	Control[2]	Break	CPT[2]
min	9	10	15	10	15	9	10	15	10

[1] SP and PT randomized
[2] Control and CPT randomized

2.10 Data analysis
Grand average EPs (C_Z-A_1A_2) were obtained of each of the five stimulus amplitudes or NoP for all protocols. Trials with an EOG artifact exceeding ±70μV in a time window of 60-400 ms post stimulus were rejected. Furthermore, mean NRS scores were obtained at all fives stimulus amplitudes (SP) or at all five NoP (PT) for both CPT and control.

3 Results

3.1 NRS scores of SP
Mean NRS scores were obtained for each of the five stimulus amplitudes. Mean NRS scores for SP with control or CPT are shown in figure 1 A. The results show a decrease of NRS scores by CPT. The (almost) linear relationship between NRS scores and stimulus amplitudes was unchanged by CPT.

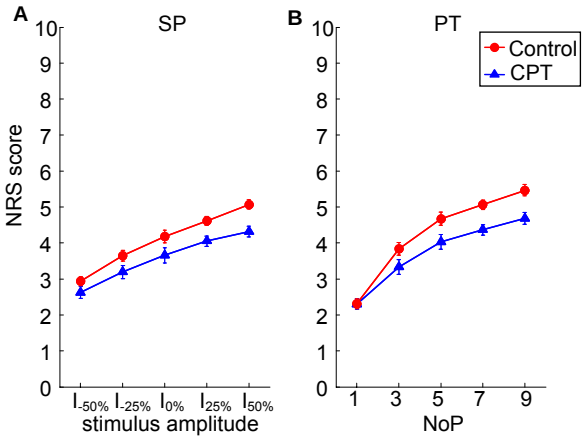

Figure 1: Mean NRS scores (±SEM) of five stimulus amplitudes for SP (A) and all five NoP (B) with CPT or control.

3.2 NRS scores of PT
Mean NRS scores for each of the five NoP for control and CPT are shown in figure 1B. The NRS scores for CPT lie below control scores. Except the lowest scores. Both curves clearly show a curved effect.

3.3 EPs of SP
Grand average EPs of five stimulus amplitudes in combination with control or CPT protocol are shown in figure 2A and 2C respectively. The relationship between P300 EP component amplitude and stimulus amplitudes (figure 3A) is comparable to the relationship between NRS and stimulus amplitude (Figure 1A). EP amplitudes of the P300 decreased by CPT (figure 3A).

3.4 EPs of PT
Figures 2B and 2D show grand average EPs of the five NoP with control or CPT. A stimulation artifact can be distinguished during the first milliseconds of the EP, lasting up to 45 ms for stimulation with 9 pulses. Figure 3B shows the relationship between P300 EP amplitude and NoP for both control and CPT protocol. It is comparable to the relationship between NRS scores and NoP. Again the EP amplitudes decreased under CPT protocol. Besides the P300, also the N150 EP amplitude decreased by CPT.

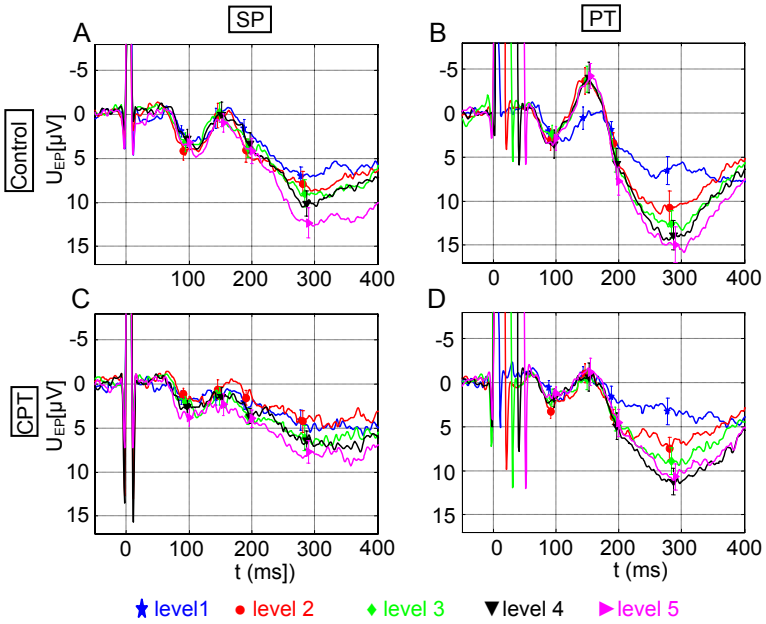

Figure 2: Grand average EPs (±SEM) of five stimulus amplitudes in combination with control (A) and CPT (C). Grand average EPs (±SEM) of five NoP with control (B) or CPT (D). Levels mentioned in the figure correspond to stimulus amplitude (SP) and NoP (PT).

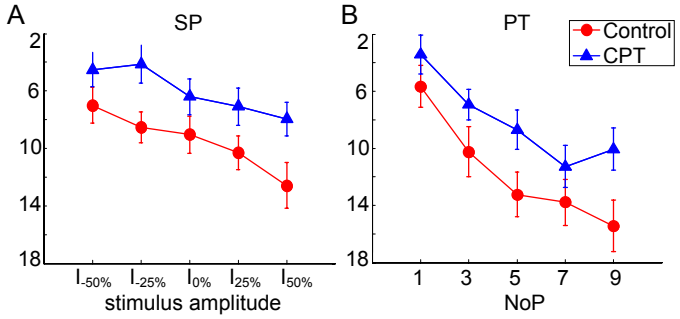

Figure 3: EP amplitude (±SEM) of P300 EP component for SP (A) and PT (B) in combination with control or CPT protocol.

4 Discussion & Conclusion

In the present study we showed that both NRS scores and EP component amplitudes decreased by applying the CPT protocol, both for SP and PT. The decrease by CPT is consistent with results in the literature for laser stimulation with one stimulus strength [6]. In the current study we applied five stimulus amplitudes (SP) or five NoP (PT). The linear effect of stimulus amplitude on NRS scores and the P300 for SP and the curved effect for PT were not changed by CPT. The inhibitory effect of CPT seems not equal for all NoP or stimulus amplitudes. The apparently inhibiting effect by CPT of both SP and PT can be ascribed to activation of endogenous pain modulation by DNIC. Pain patients show impairment of DNIC and abnormal endogenous modulation [2, 7]. Therefore these results are promising for further research to changes in the nociceptive system in the of pain patients.

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