Istraživanje je obuhvatilo - mediated mainly by neurotransmitters - serotonin, analgesia [1]. It operates through several mechanisms: mechanism of modulation is known as endogenous analgesia can be examined in humans in experimental conditions and can be studied in vivo or in vitro. Intra-neuronal potentials and reliability of conditioned pain modulation effect in healthy population by application of a conditioning contact heat stimulus, a test stimulus, and heat and pressure applied to the low back region as a test stimulus. Material and Methods. The study included 33 healthy subjects (average age 25.73 ± 5.35 years). Pressure and heat pain thresholds were examined on the paravertebral musculature of the low back as test stimuli. Contact heat was used on the contralateral forearm as a conditioning stimulus. Conditioned pain modulation was calculated as the difference between pain thresholds after and before conditioning stimulus application. To assess the reliability, identical testing was performed 14 ± 2 days later. Results. The pressure and heat pain thresholds, after the conditioning stimulus were significantly higher compared to pain thresholds obtained before the conditioning stimulus (101.63 N/cm² ± 45.21 N/cm² vs 82.15 N/cm² ± 36.15 N/cm², t = -7.528, p < 0.001 and 47.08°C ± 2.19°C vs 45.00°C ± 3.05°C, t = -6.644, p < 0.001, respectively). The reliability of the same protocol, measured 14 ± 2 days after the previous testing, showed good reliability of the pressure pain threshold (intraclass correlation coefficient = 0.636, 95% confidence interval 0.240 - 0.825), and fair of the heat pain threshold (intraclass correlation coefficient = 0.435, 95% confidence interval 0.070 - 0.713). Conclusion. Conditioned pain modulation was successfully induced by contact heat applied via a thermode, a conditioning stimulus. The reliability of this method of testing proved to be fair when it comes to the heat pain threshold and good when it comes to the pressure pain threshold. Key words: Pain Measurement; Pain; Pain Threshold; Heating; Pressure; Conditioning (Psychology); Nociception; Analgesia; Back Muscles

Summary

Introduction. The objective of the study was to determine the potentials and reliability of conditioned pain modulation effect in healthy population by application of a conditioning contact heat stimulus, and heat and pressure applied to the low back region as a test stimulus. Material and Methods. The study included 33 healthy subjects (average age 25.73 ± 5.35 years). Pressure and heat pain thresholds were examined on the paravertebral musculature of the lower back as test stimuli. Contact heat was used on the contralateral forearm as a conditioning stimulus. Conditioned pain modulation was calculated as the difference between pain thresholds after and before conditioning stimulus application. To assess the reliability, identical testing was performed 14 ± 2 days later. Results. The pressure and heat pain thresholds, after the conditioning stimulus, were significantly higher compared to pain thresholds obtained before the conditioning stimulus (101.63 N/cm² ± 45.21 N/cm² vs 82.15 N/cm² ± 36.15 N/cm², t = -7.528, p < 0.001 and 47.08°C ± 2.19°C vs 45.00°C ± 3.05°C, t = -6.644, p < 0.001, respectively). The reliability of the same protocol, measured 14 ± 2 days after the previous testing, showed good reliability of the pressure pain threshold (intraclass correlation coefficient = 0.636, 95% confidence interval 0.240 - 0.825), and fair of the heat pain threshold (intraclass correlation coefficient = 0.435, 95% confidence interval 0.070 - 0.713). Conclusion. Conditioned pain modulation was successfully induced by contact heat applied via a thermode, a conditioning stimulus. The reliability of this method of testing proved to be fair when it comes to the heat pain threshold and good when it comes to the pressure pain threshold. Key words: Pain Measurement; Pain; Pain Threshold; Heating; Pressure; Conditioning (Psychology); Nociception; Analgesia; Back Muscles

Introduction

The pain perception is regulated by the intrinsic pathways of pain modulation which can increase or reduce the harmful afferent stimulus. The inhibitory mechanism of modulation is known as endogenous analgesia [1]. It operates through several mechanisms mediated mainly by neurotransmitters - serotonin, dopamine, and noradrenaline [2]. In 1979, Le Bars et al. described the inhibitory mechanism, diffuse noxious inhibitory controls (DNIC). They proved a decrease of the rats’ response to pain in the neurons of the posterior horn of the spinal cord after application of nociceptive stimulus distant from the excitatory peripheral receptive field [3]. Today, endogenous analgesia can be examined in humans in experimental...
The study included 33 healthy subjects, students of the Faculty of Medicine of the University of Novi Sad, with an average age of 25.73 ± 5.35 years. The research was approved by the Ethics Committee of the Faculty of Medicine, University of Novi Sad and all respondents signed an informed consent.

The research inclusion criterion was age above 18 years. The exclusion criteria were: chronic pain or any other current pain (headache, injury, etc.), diabetes, uncontrolled arterial hypertension, cardiovascular or pulmonary disease with complications, psychiatric disorders, use of analgesics, tranquilizers, antidepressants, anticonvulsants, not understanding the task.

All subjects were instructed not to take analgesics or alcohol for 24 hours before taking part in the study, to get enough sleep before the examination, not to have coffee/caffeine-containing products for 4 hours before testing, and not to get into any heavy physical activity.

After the respondents were informed and acquainted with the procedure and devices, the testing started. In the first part of the research, we investigated the pressure pain threshold (PPT) and the heat pain threshold (HPT). A digital algometer was used for PPT (Wagner Instruments, FDX-50), with rubber tip of 1cm², at the paravertebral musculature of the lumbar segment (2 cm lateral to the spinous process L3) [13]. The pressure was gradually increased at the rate of 5 N/s until respondents said to stop, after the feeling turned painful, the point when we recorded the N/cm² value. There were 3 measurements at each point with 10s intervals, and the average value was recorded as the final. Tests were randomized between left and right sides [12].

The HPT testing was performed using a device with advanced thermal stimulation (ATS) Thermode of 30 x 30 mm (Pathway Pain and Sensory Evaluation System, Medoc Ltd, Ramat Yishai, Israel) at 2 points: 1) paravertebral musculature of the lumbar segment (2 cm lateral from spinous process L1) and 2) on the proximal volar side of the opposite forearm (C8 dermatome) [13]. Tests were randomized between the left and right sides [12]. When testing HPT, the initial temperature of 32° C was increased at a rate of 0.7° C/s. The examinees pressed the stop button as soon as the feeling of warmth turned into a burning sensation, feeling of puncture or pain. At that moment, the temperature was lowered to the initial temperature at the speed of 7° C/s. Four heat stimulations were performed with 10s intervals, and the last three measurements were taken into account for the final HPT value. The pain thresholds for heat on the forearm were first tested while the subject was comfortably lying on the back. Then the examinees laid down on the stomach, and PPT was examined first, followed by HPT on the lumbar segment at previously defined places.

After examining the pain thresholds, a 15 minutes pause was made, after which testing of effects of CPM was performed. In order to induce and test CPM, stimulation of the conditioning stimulus (CS) - contact heat on the proximal volar side of the opposite forearm (C8 dermatome) with the ATS thermodynamic pathway device was performed while the subject was lying on the stomach. The intensity of CS was determined individually as the HPT value (determined by the original measurement on the same

**Abbreviations**

CPM – conditioned pain modulation  
PPT – pressure pain threshold  
HPT – heat pain threshold  
ATS – advanced thermal stimulation  
CS – conditioning stimulus  
NPS – numerical pain scale  
ICC – intraclass correlation coefficient  
SEM – standard error of measurement  
TS – test stimulus

conditions using a paradigm of conditioned pain modulation (CPM) [4]. The CPM involves lowering the intensity of pain or boosting the threshold of pain to a particular stimulus (test stimulus), during or after the application of another painful stimulation (conditioning stimulus) applied to a distant part of the body [4, 5]. Healthy people are generally able to successfully inhibit pain which is an indicator of the efficacy of CPM, while in patients with chronic pain CPM shows a lower efficiency [6]. The studies have shown a dysfunctional CPM in different chronic painful conditions, such as fibromyalgia [7], temporomandibular disorders [8], irritable bowel syndrome, migraine, tension headache [9], back pain [10].

There are numerous CPM research protocols which differ by the type of test and conditioning stimulus of the subject tested, temporary characteristics (parallel and sequential simulation), and pain parameters on stimulus test (pain resistance, intensity, and temporal summation). The most commonly used type of conditioning stimulus is cold pressor arm wrap test. Another frequent method is hot water immersion. There are numerous modalities used as stimulus tests - thermal, mechanical, electrical, chemical, all of them applied to different parts of the body [5]. However, there is no gold standard when it comes to CPM research, nor any proof that a specific protocol is superior to another [11]. Even though there are many conditional pain modulation research protocols, only a few have examined this effect by applying the test stimulus to low back region [12–14]. In their study, Gerthard et al. claimed that it was more clinically relevant to apply stimulus test on the area which already exhibited pain [12].

The objective of the study was to determine the potentials and reliability of conditioned pain modulation effect in a healthy population by using the contact heat as conditioning stimulus, and heat and pressure applied to the low back region as a test stimulus. We have put forward the hypothesis that a significant effect of conditioned pain modulation can be induced with good reliability.

**Material and Methods**

The study included 33 healthy subjects, students of the Faculty of Medicine of the University of Novi Sad, with an average age of 25.73 ± 5.35 years. The research was approved by the Ethics Committee of the Faculty of Medicine, University of Novi Sad and all respondents signed an informed consent.
In order to guarantee safety of the subjects, as well as activate the nociceptors, adjustments have been made in the following order: 1. if the HPT + 1° C was higher than 47° C, CS temperature was lowered to 47° C. 2. in subjects where HPT + 1° C was below 40° C, CS was adjusted to 40° C [12]. The CS stimulation starting temperature was 32° C and kept increasing at the rate of 0,7° C/s until the predetermined temperature that lasted 120s (Ramp and Hold program) [12, 13]. During those 120s subjects have measured the pain in 30s intervals on a numerical pain scale (NPS) from 0 – 100, in which case 0 meant “no pain” while 100 meant “worst imaginable pain” [13]. In case a subject could not tolerate the assigned temperature or have measured the pain with > 90/100 temperate was lowered by 0,5° C although keeping pain intensity above 45/100 on NPS. This way we have guaranteed the safe CS that is intensive enough to cause CPM effect [13]. In case some of the subjects have declared pain less than 45/100 stimulation was interrupted and the temperature was increased by 1° C until the pain has reached at least 45/100 [13]. After 120s, the temperature went back to default level at the rate of 7° C and CS stimulation was finalized [13]. One minute after the end of CS (sequential paradigm), second test stimulus (TS2) in the lumbar area (PPT first then HPT) were tested again [11, 12]. Two types of stimuli have been used as test stimulus: PPT and HPT measured in a lumbar segment. For values of the first test stimulus (TS1) PPT and HPT values were taken during pain threshold on paravertebral musculature of the lumbar segment [11, 13, 15]. The difference between TS values after and before CS (TS2 - TS1) resembled the values of CPM. Positive value underscores the existence of CPM effect (elevation of pain threshold) while negative shows nonexistence of CPM effect (pain facilitation) [11].

In order to test the reliability of this protocol, a retest was made, and the same subjects were called for identical testing after 14 ± 2 days. A subgroup of 18 subjects, underwent the same protocol 30 days after the retest, except they did not receive CS. In this way, we wanted to test the magnitude of the error and to investigate the difference between the results of the HPT and PPT, 15 minutes later. The normality and distribution of the sample were evaluated for skewness and kurtosis. Paired-Samples T-test was used in order to investigate differences between TS threshold before and after CS. The same test was used to compare CS temperatures and pain intensities at the test and retest after two weeks. For reliability testing intraclass correlation coefficient (ICC) (two way mixed, absolute agreement) was used [16]. The ICC values < 0,4 were interpreted as poor, 0,4 - 0,59 as fair, 0,6 - 0,75 as good, and > 0,75 as excellent reliability [17–19]. P values ≤ 0,05 were considered statistically significant.

For the subgroup of 18 subjects who underwent testing without CS, the standard error of measurement (SEM) was calculated according to the formula SEM = SD* (1-ICC). This measure was used to estimate the range of measurements that might have occurred in subjects after repeated testing [20]. The value of the SEM was added to the HPT and PPT and was transformed into percentages to show the highest limit of SEM in repeated measurement. Data analyses were performed using the statistical package for the social sciences (SPSS) 23.

**Results**

The sample included 33 students and the majority (23) were female (69.7%). Their average body weight was 66,44 ± 16,05 kg, average height 173,03 ± 9,28 cm, and body mass index (BMI) 22,01 ± 3,93 kg/m². The average conditioned heat stimuli temperatures and average pain intensities on the test and retest are shown in Table 1. An average temperature of the CS was significantly higher on the retest, although this was not accompanied by significantly higher pain intensity reported by subjects.

Significantly higher pain thresholds were achieved after CS for both pressure and heat at test and retest after 14 days (Table 2). The PPT after CS was higher (13.79%) on the retest (23.71%) compared to the basic

| Test/Test (n=33) | 0s  | 30s  | 60s  | 90s  | 120s | Average |
|-----------------|-----|------|------|------|------|---------|
| 45,3±1,7        | 60,3±10,9 | 61,4±11,6 | 65,8±13,1 | 68,0±18,9 | 71,7±17,6 | 65,4±11,9 |
| Retest/Ponovljen test (n=32) | 46,0±1,3 | 63,4±12,9 | 64,8±12,5 | 67,5±14,6 | 71,1±14,6 | 73,2±15,1 | 68,0±11,6 |
| t               | -2,432 | -1,824 | -1,722 | -0,956 | -1,751 | -0,913 | 0,368 |
| p               | 0,021 | 0,078 | 0,095 | 0,347 | 0,090 | -1,782 | 0,085 |
| Intraclass correlacion coefficient† | 0,675 | 0,737 | 0,526 | 0,720 | 0,815 | 0,821 | 0,771 |

Table 1. Pain intensity during conditioning stimulation

**Table 1. Intenzitet bola tokom stimulacije uslovljavajućim stimulusom**

### **Results**

The sample included 33 students and the majority (23) were female (69.7%). Their average body weight was 66.44 ± 16.05 kg, average height 173.03 ± 9.28 cm, and body mass index (BMI) 22.01 ± 3.93 kg/m². The average conditioned heat stimuli temperatures and average pain intensities on the test and retest are shown in Table 1. An average temperature of the CS was significantly higher on the retest, although this was not accompanied by significantly higher pain intensity reported by subjects.

Significantly higher pain thresholds were achieved after CS for both pressure and heat at test and retest after 14 days (Table 2). The PPT after CS was higher (13.79%) on the retest (23.71%) compared to the basic
values. The PHT after CS was higher (2.43%) on the retest (4.62%) compared to the basic values.

The ICC was good for the PPT (ICC = 0.636), and fair for the PHT (ICC = 0.435). Table 3 provides more detailed results.

The calculated ICC for the PPT was 0.98, while for the HPT it was 0.96. In the subgroup of 18 subjects, who underwent two consecutive testing without CS, the SEM was 4.09 N/cm² and 4.08 N/cm² for the PPT, in percentage 105.01% and 104.99% (after 15 minutes without CS). The SEM for the HPT was 0.5°C and 0.43°C and in percentage we got 101.08% and 100.93% (after 15 minutes without CS). The average SEM percentage for the PPT was 105.00% and 101.00% for the HPT. It was determined that any CPM value over 5% for the PPT and over 1% for the HPT indicated effect greater than the inherent error of measurement. The further calculation showed that a significant CPM for the PPT was obtained in 28 (84.8%) and 31 (93.9%) subjects for the HPT.

Discussion

Although there are many different protocols for testing CPM, the data are insufficient to support a significant CPM for the PPT was obtained in 28 (84.8%) and 31 (93.9%) subjects for the HPT.

Table 3. Intraclass correlation coefficient and 95% confidence intervals in test-retest reliability

| Test/Retest (n=33) | PPT† (N/cm²±SD) | 82.15±36.15 | 101.63±45.21 | 19.48±14.86 | -7.528 <0.001 |
|---------------------|------------------|-------------|-------------|-------------|-------------|
|                     | HPT‡ (C±SD)      | 45.00±3.05  | 47.08±2.19  | 2.08±1.80   | -6.644 <0.001 |

Table 3. Description of the stimulation scores before and after the conditioning stimulus

| Test stimulus | Before CS* | After CS* | CPM** response (After CS* – Before CS*)/odgovor (Pre CS* – Posle CS*) |
|---------------|------------|-----------|--------------------------------------------------|
| Uslovljavajući stimulus | Pre CS* | Posle CS* | Before CS*/CPM** |

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Table 3. Intraclass correlation coefficient and 95% confidence intervals in test-retest reliability
for several hours. There were no other adverse events reported, and all subjects successfully completed the planned protocol.

The issue regarding non-responders is very important [23]. Locke et al. found that a significant CPM effect was an increase in PPT values from baseline greater than 5.3% [27]. This percentage represents the calculated inherent error of measurement. In our study, we found that SEM was 5% for the PPT and 1% for the HPT, which was similar to results of Locke et al. [27]. Our results showed that CPM effect was reached in 85% of subject for the PPT that was by 10% lower than found by Locke et al. [27], while CPM effect for HPT was reached in 94% of subjects. Interestingly, CPM effect was present in several subjects for the HPT, but it was lacking for the PPT and vice versa.

In the majority of studies, immersion into the hot or cold water was a preferable option for the CS as it has shown better reliability [9, 18, 23]. However, usage of thermode as CS has its benefits, such as the ability to test pain thresholds in the specific region such as the low back region. Parallel paradigm is more frequently used compared to sequential paradigm [9, 23], although there is no clear recommendation which one is more reliable [23]. One can argue that the simultaneous application of two painful stimuli might confuse the examinees and make it harder to estimate the pain thresholds or pain intensities. Therefore, we used a sequential paradigm, where we divided CS and TS with one-minute pause in between. It is estimated that CPM effect probably lasts 10 – 15 minutes after CS [26]. During the research, we were able to finish all intended testing in a time frame of less than 5 minutes including a pause of one minute after CS. Time periods between test-retest vary in the literature from 2 days to 3 months [28–32]. We have decided to perform the retest after 14 ± 2 days.

Although thermode in our protocol was used on a relatively small area (9 cm²), we obtained good ICC scores for CPM calculated via PPT and fair ICC scores for CPM calculated via HPT. These results are encouraging, having in mind that the previous studies showed poor reliability for contact heat as CS [18, 23]. It could be that the pain stimulus duration, as well as higher pain intensity of the CS in our study, was the reason why we obtained better reliability compared to the previous studies that used contact heat as CS. Some evidence suggest that pain intensity of the CS is an important factor for CPM magnitude [33].

In some of the previous studies, temperature used to provoke predetermined pain intensity was recorded, and the capacity of the CPM was calculated according to these values [18]. Other authors claim that pain threshold, which was used in our study, was a superior method for CPM testing [23]. The authors are searching for more practical and less time consuming protocols [18]. However, this must not decrease the reliability.

Conclusion

Conditioned pain modulation was successfully induced by contact heat applied via thermode as a conditioning stimulus. However, the reliability varied from good for pressure pain threshold as a test stimulus to fair for the heat pain threshold as a test stimulus. This protocol could be beneficial for testing different groups of patients, being a simple, quick and safe procedure. Therefore, we suggest further testing and recommend a comparison of the conditioned pain modulation phenomenon between genders and different age groups, as well as testing its reliability in larger samples.

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