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Thermal pain perception during different satiety levels in males and females across follicular and luteal phases of the ovarian-menstrual cycle

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Abstract: Nowadays it is known that sex hormones play an important role not only in the reproductive system but also in thermoregulation, somatosensory control, and pain perception. Several studies have shown that women are less tolerant of pain and have higher sensitivity and predisposition to somatization and pain chronification. In addition to sex, feeding status is also an essential factor for pain perception. Metabolic factors and glucose levels may play a role in the sensation of pain. In this paper, we report an evaluation of thermal pain thresholds induced by heat and cold stimulation in males and females during primary (pre-resorption) and secondary (metabolic) satiety. The obtained data showed that in both sensory-motor satiety and metabolic satiety, the heat pain threshold was significantly higher in males than in females in the follicular and luteal phases of the ovarian-menstrual cycle. Further studies are needed to detect more details on the influence of food satiety levels on pain perception regarding sex differences.

Keywords: pain, thermal pain, primary satiety, secondary satiety, phases of the ovarian-menstrual cycle.

Introduction

According to the International Association for the Study of Pain (IASP), pain sensation is a protective mechanism, which relies on subjective and objective experience, related to actual or possible tissue damage [1].

Pain is an essential protective mechanism coupled with urgency to cease the irritating factor's action. The phenomenon of pain still remains one of the most important challenges in medicine, which often leads to disabilities and worsened life quality in the human population.

Recently, gender-associated differences have been the subject of a number of studies, which revealed, that females compared to males are more sensitive to experimental pain and postoperative pain than males [2,3]. In addition, some data suggest that females are more prone to chronic pain during conditions, such as fibromyalgia, irritable bowel syndrome, temporomandibular pain, and arthritis [4-6]. These findings raise suspicion that sex differences should be thoroughly investigated.

Different factors contribute to sex differences in pain perception. For example, some studies show that females tend to catastrophize their pain more [7], which can be attributed to sociocultural reasons. Besides, some data suggest that women report different findings in terms of pain threshold and sensitivity throughout the ovarian-menstrual cycle. Nowadays, this variability is thought to be dependent on sex hormones and psychosocial factors [8,9].

In terms of biology, sex hormones play an important role not only in the reproductive system but also in thermoregulation, feeding, memory formation, and somatosensory control.

Herren first noted the relationship between hormonal levels and pain perception in 1933 [10]. Some studies [11,12,13] show that women are less tolerant of pain and have higher sensitivity and predisposition to somatization. In addition, some data show that during early menopause, increased pain perception is caused by diminished levels of estrogens [14], but on the other hand, the findings of different studies are controversial: in 2012, Stening and colleagues carried out the study of pain in females undergoing in vitro fertilization and revealed, that in contrast to abundant reports from animal studies of gonadal steroid hormone influence of pain, no measurable effects were seen despite the major variations in serum 17-beta-estradiol induced by IVF-treatment [15]. Estrogens are involved in pain transmission via neuroanatomic pathways at the central and peripheral levels, and the brain is one of the target organs of estrogen.

According to other studies, there is a significant correlation between increased pain perception, increased levels of progesterone and reduced levels of estrogens associated with the luteal phase (16). The mechanism possibly relies on the upregulation of opioid receptors and the activation of endogenic opioid neurotransmission. In contrast, decreased estrogen levels in the thalamus and amygdala downregulate opioid receptors, resulting in associated hyperalgesia [17].

As the level of estrogens by itself varies during the ovarian-menstrual cycle, peaking in the follicular phase in response to follicular stimulating hormone (FSH) and decreasing after ovulation, in the luteal phase, in response to diminished concentrations of follicular stimulating hormone and luteinizing hormone, our team decided to take hormonal factor into consideration and subdivide the female cohort according to the ovarian-menstrual cycle, by using the questionnaires prior to the experiment.

Thermal perception is essential for somatosensory organs because it combines the central and peripheral nervous system components. It is considerable, that warmth and cold are perceived as two distinct sensations. All nociceptors have the ability to feel pain, but dramatically low temperatures are required to activate some nociceptors. This may be caused by the non-specific response of the tissues to freezing.

Recent studies reveal, that in addition to biological and psychosocial mechanisms, pain perception can be altered by satiety levels as well [18]. Food ingestion results in satiety, sleepiness, and several physiological effects, such as increased heart rate and cardiac output [19]. Metabolic factors and glucose levels may play a role in the sensation of pain. According to some studies, certain foods, such as those rich in lipids, can decrease cold pain sensations in healthy individuals [19]. Also, there is a link between sweet products and increased tolerance to pain [20], but on the other hand, other data suggest decreasing pain threshold in hyperglycemic states [21].

Glucose is thought to be linked to an endogenous opioid, endorphin, which can modulate physical and emotional stress and pain in humans [22]. Endogenic opiates decrease pain. In vertebrates, the opioid system stimulates gastric juice and digestive enzyme secretion, which may have analgesic effects. In addition, endogenic opioids decrease emotional background, which also plays a role in the response to painful triggers. Together with endogenic opioids, cholecystokinin is also released, which mediates sedative and analgesic effects and even increases opioid production [23,24].

The earlier research, which aimed to study the role of feeding on pain perception, presented that the participants had higher pain sensitivity during starvation, which used to diminish over time after feeding. As the experiment described above included only 16 participants (8 males, 8 females), the data was not sufficient for a reliable conclusion about gender differences related to satiety. The later study investigating satiety-dependent changes in pain perception in which 32 males and 30 females took part, revealing significant differences between males and females, in thermal pain threshold parameters during starvation [25].

Therefore, the main goal of our study was to assess pain perception induced by thermal irritation in males and females in follicular and luteal phases of the ovarian-menstrual cycle during different satiety levels: during starvation, primary satiety and secondary satiety. The cohorts of males and females were subdivided according to 3 stages of satiety, as each of them is coupled with different conditions in human body. The primary (sensory-motor, pre-resorptive) satiety is defined as the state suppressing the hunger center, even before nutrients are transported to the blood. The sensory-motor satiety is converted into metabolic (secondary) satiety, once the end-products of food digestion are transported into the blood and their high concentrations are detected.

In previous stages of our research, we studied the pain perception of males and females in the follicular and luteal phases of the ovarian-menstrual cycle during physiological starvation. We found higher sensitivity to pain in women than in males. There was also a difference between the different phases of the ovarian menstrual cycle [26]. Thus, the purpose of our upcoming study was to evaluate the pain threshold induced by cold and warm stimuli in males and females during primary (pre-resorptive) and secondary (metabolic) satiety. The reliable data about the correlation between pain sensitivity and various satiety states can become essential for filling the gaps in our general knowledge about the pain phenomenon and improving individual pain management resources and diagnostic tools.

Materials and methods

Participants

The study sample comprised 50 volunteer students (F=25, M=25) aged 18-23, (mean age 20,5 ± 2,5). Menstrual cycle phases were determined using questionnaires and calendar methods. 7-11th days of the ovarian menstrual cycle were assessed as the follicular phase, while the 18-22nd days was assessed as the luteal phase. Patients with an irregular menstrual cycle (less than 21 days, and/or more than 35 days apart) were excluded from the study.

The main selection criterion for the participants was their health status. Those without chronic pain; obesity, cardiovascular, respiratory, endocrine, and other disorders; and chronic use of any medication (including contraceptive pills) were selected for participation in the study. The presence or absence of the aforementioned disorders was evaluated using electrocardiography, spirometry, height, weight, arterial blood pressure, and BMI of the participants.

Prior to the start of the study, participants were given information about their rights and could refuse to participate in the study at any stage. Written informed consent was obtained from all participants. All study procedures and protocols were approved by the Biomedical Ethics Committee of the Tbilisi State Medical University. The study was conducted in compliance with all the requirements and regulations of the Ethical Guidelines for Pain Research in Humans of the International Association for the Study of Pain (IASP) (www.iasp-pain.org/resources/guidelines/ethical-guidelines-for-pain-research-in-humans/).

This study was performed in two stages: during primary satiety and secondary satiety. The types of satieties were distinguished from one another, as they characterize different states in the human body. The first phase was held in primary (sensory-motor) satiety, 20-30 minutes after the last meal, and the second phase in secondary (metabolic) satiety, 60-90 minutes after the last meal. The meals with mixed, standardized nutrients were provided by our team and given to participants.

Each phase of the study was performed in the morning, at 9 am. The experiment took place in an isolated, sound-proof space. The participant was placed in a comfortable armchair. The duration of the study was approximately 2 hours: 30 min after the meal for assessing primary satiety and 90 min after the meal to assess secondary satiety.

Procedures

Thermal pain sensitivity was assessed using the computer-controlled tool Pain & Sensory Evaluation combined system PATHWAY (Medoc, LTD, Ramat Yishai, Israel), in which probands were given hot/cold stimuli, and thermal sensitivity and pain thresholds were simultaneously detected. A 3x3 cm flat probe was fixed to the sole of the right palm of the subject with rubber. The intensity from the baseline (comfort) temperature 32 °C, was getting increased by 0.5 °C in a second until proband was used to hit the button for detecting heat/cold threshold. The maximum temperature was +55 °C, whereas the minimum temperature was 0 °C (to prevent tissue damage). To avoid sensitization/adaptation of skin receptors, the time gap between stimulus delivery was 10 s.

The participants were given stimuli in the following sequence: four episodes for detecting heat/cold sensitivity, three episodes for the threshold to cold pain, and three episodes for the heat pain threshold. The thermode moved across the skin to decrease skin adaptation; therefore, the area of skin stimulation made up 6x6 cm. Prior to the main procedure, experimental stimuli were provided to the probands to avoid emotional responses. Instruction on the procedure was provided to the probands prior to the experiment.

The findings were assessed quantitatively by the probands automatically by pressing the button when they perceived heat/cold and pressing the button in another (left) hand when the sensation was converted into pain. Thermal alterations in thermode and evaluation of mean findings (in °C) for each parameter were managed according to a previous study [26].

Statistical analysis

Data were tested for normal distribution. The mean values for each of the responses for detection thermal sensation thresholds, and thermal pain thresholds were calculated. Data were subjected to repeated measures analysis of variance (ANOVA). Comparisons between groups were made by paired t-test. Kruskal–Wallis ANOVA and subsequent post hoc Tukey test was used to assess differences between groups. The data are expressed as mean ± s.e.m. Statistical significance was acknowledged if $p < 0.05$. The statistical software utilized was InStat 3.05 (GraphPad Software, Inc., San Diego, CA, USA).

Results

According to the obtained data, the differences between male and female thresholds in both, follicular and luteal phases are significant. In particular, in sensory-motor satiety, the warmth pain threshold is significantly high in males, compared to females in both, follicular ($t = 6.23$, $p < 0.01$) and luteal phases ($t = 4.62$, $p < 0.05$). As for metabolic satiety, the differences between males and females are also significant in follicular ($t = 7.17$, $p < 0.01$) and luteal phases ($t = 3.53$, $p < 0.05$) (Figure 1).

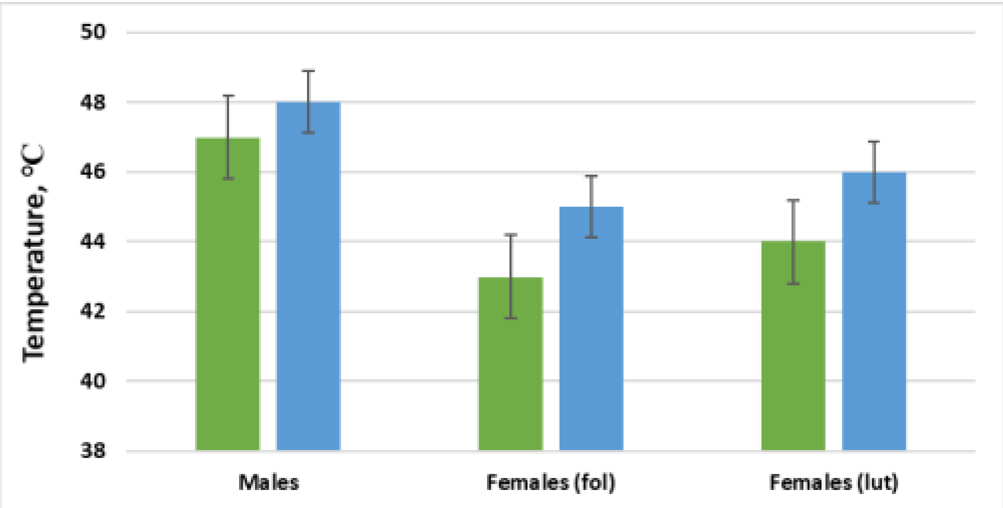

Figure 1Heat pain thresholds in males and females (follicular/luteal phases) in sensory-motor and metabolic satieties. In both phases of satiety, the heat pain threshold is significantly higher in males, than in females in follicular/luteal phases.

As for assessing the cold pain, there is not a significantly high threshold in males compared to females in follicular phases of the ovarian-menstrual cycle in both sensory-motor satiety and metabolic satiety ($P > 0.05$), but not for differences in luteal phase for sensory motor satiety ($t = 6.84$, $p < 0.01$) and for metabolic satiety ($t = 6.59$, $p < 0.01$) (Figure 2).

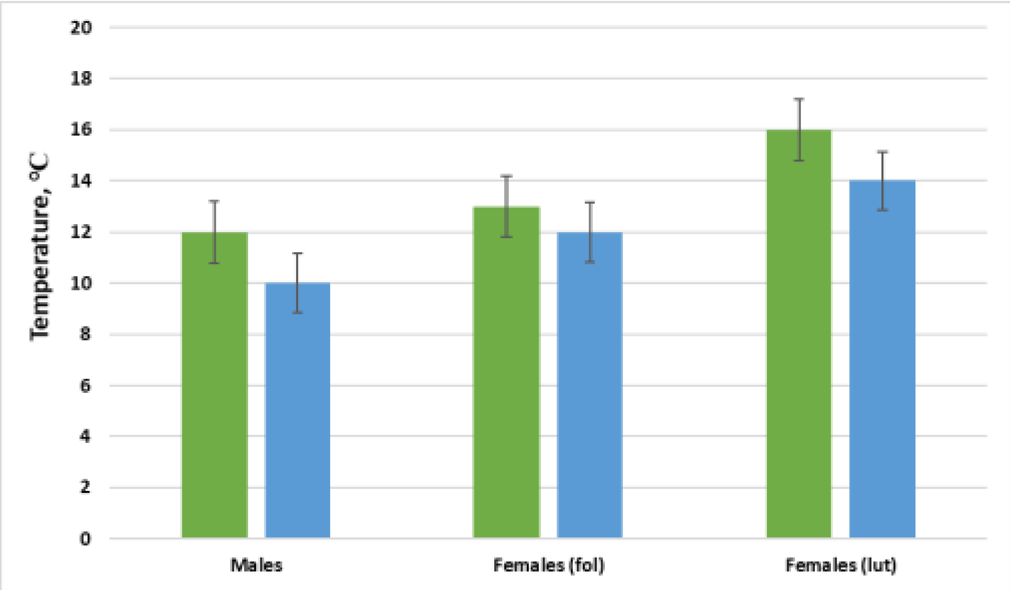

Figure 2-Cold pain thresholds in males and females (follicular/luteal phases) - insignificant difference between males and females in follicular, but significant-between males and females in luteal phase, during sensory-motor and metabolic satieties

Discussion

According to recent studies, the effect of estrogen on pain perception can be contradictory and can be explained by the specific mechanism of action of estrogen in various cells and tissues [14]. The findings of the latter research correlate with the data of our previous study [26] showing that males, compared to females, have a higher mechanical pain threshold and in addition to this, the pain perception threshold in the follicular phase can be higher than in the luteal phase. The findings also coincide with data showing that irritation caused by cold, heat, and ischemic pain shows significantly higher pain perception in females. However, changes in pain perception due to the ovarian-menstrual cycle have not been noted [27]. The absence of an ovarian-menstrual cycle influence on pain sensation has not been observed in other studies [28]. In other experiments, it was noted that there was increased pain perception in the premenstrual period compared to the ovulatory phase, and some data confirmed that a high level of estrogen correlates with increased pain sensitivity [29].

As according to our experiment, pain perception seems to be affected by changing satiety levels, our findings in the future can result in altered approaches in patient-care services. Assessing whether the patient is in primary or secondary satiety, can assist physicians to improve pain management tools and diminish the risks of pain chronification.

To actively use the results of our study in clinical medicine, it is compulsory for investigation within the field to continue, which can become essential for creating an algorithm to manage chronic pain. This can be life-changing for healthcare workers to prevent disabilities caused by chronic pain, which in turn can improve the quality of life of patients with chronic illnesses.

Data Availability Statement

The data is available upon request to interested researchers.

Disclosure of Interest

The authors report there are no competing interests to declare.

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Figure Captions

Figure 1. Heat pain thresholds (°C) in males and females (follicular and luteal phases of ovarian-menstrual cycle) in sensory-motor and metabolic satieties. Green columns for sensory-motor satiety, and blue columns for metabolic satiety. Notes: In sensory-motor satiety, the heat pain threshold is significantly high in males, compared to females in follicular phase ($p < 0.01$) and luteal phase ($p < 0.05$). For metabolic satiety, the differences between males and females are also significant in follicular phase ($p < 0.01$) and luteal phase ($p < 0.05$).

Figure 2. Cold pain thresholds (°C) in males and female (follicular and luteal phases of ovarian-menstrual cycle) in sensory-motor and metabolic satieties. Green columns for sensory-motor satiety, blue columns for metabolic satiety. Notes: The differences in cold pain threshold between males and females' groups in follicular phase in both sensory-motor satiety and metabolic satiety are not significant ($P > 0.05$). However, these differences between males and females' groups in luteal phase are significant in both sensory-motor satiety and metabolic satiety ($P < 0.01$).