Effect of stress on pain perception in young women

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ABSTRACT

الأهداف: تحديد تأثير التوتر بمختلف مسبباته على عتبة الشعور بالألم (PPT) ومعدل تحمل الألم (PTOL) لدى البالغات من الإناث، ومقارنة مسببات التوتر المختلفة من حيث قدرتها على التأثير على عتبة الشعور (PPT) بالألم ومعدل تحمل الألم (PTOL). كذلك دراسة العلاقة بين مؤشر كتلة الجسم BMI وعتبة الشعور بالألم (PPT) ومعدل تحمل الألم (PTOL) لديهن.

الطريقة: أُجريت دراسة شملت 79 طالبة من طالبات السنة الثانية بكلية الطب – جامعة الملك فيصل – الدمام – المملكة العربية السعودية، خلال عام 2007م. أجريت الدراسة على الطالبة نفسها قبل وبعد تعرضها لثلاث أوساط مسببة للتوتر كل على حده. بدايةً، تم قياس عتبة الشعور بالألم (PPT) لدى الطالبات و معدل تحملهن له في غياب أي مؤثر خارجي مؤدي للتوتر عن طريق جهاز قياس الألم (algometer). ومن ثم تعرضت الطالبات إلى ثلاثة أنواع من المؤثرات الخارجية المسببة للتوتر وتم قياس عتبة شعورهن بالألم (PPT) ومعدل تحملهن له، وتم أيضا قياس مؤشر كتلة الجسم لكل طالبة، قياس ضغط الدم، نبضات القلب قبل وبعد التعرض للأوساط المسببة للتوتر. تم جمع النتائج وإجراء العمليات الإحصائية لمقارنة النتائج.

النتائج: أثبتت الدراسة أن اثنين من المؤثرات الخارجية المسببة للتوتر تزيد من عتبة الشعور بالألم (p=0.000) (PPT) وتزيد من معدل تحمل الشخص البالغ للألم (p=0.000) (PTOL). المؤثر الأول والثاني هما اختبار الغمر في الماء البارد واختبار الجهد العضلي (ISO EX)، والمؤثر الثالث هو الاختبار العملي لمادة التشريح وأدى إلى زيادة عتبة الشعور بالألم (PPT) ولكن معدل تحمل الألم (PTOL) لم يزد بالقدر الكافي لجعل النتيجة ذات جدوى إحصائية. استنتجت الدراسة أيضا، أن اختبار الغمر في الماء البارد هو الأكثر فعالية في زيادة عتبة الشعور بالألم ومعدل تحمل (p=0.009) (PPT) (PTOL)، يليه الاختبار العملي لمادة التشريح يليه أخيرا اختبار الجهد العضلي. وبخصوص زيادة معدل تحمل الإنسان البالغ للألم فإن اختبار الغمر في الماء البارد كان الأكثر فعالية في زيادته يليه اختبار الجهد العضلي يليه أخيرا الاختبار العملي لمادة التشريح.

خاتمة: برهنت الدراسة أن هناك علاقة عكسية بين مؤشر كتلة الجسم للطالبة وبين مقدار تحملها للألم بحيث أنه كلما زاد مؤشر كتلة الجسم للطالبة قل مقدار تحملها للألم. أدت هذه الدراسة إلى زيادة الفهم لما يدور داخل جسم الإنسان من آليات تحمل الألم.

Objectives: To determine the effect of physical and mental stressors on pressure pain threshold (PPT), and pressure pain tolerance (PTOL) values, and to compare these different types of stressors on its ability to affect PPT and PTOL values in young women. We also correlated body mass index (BMI) with PPT and PTOL in young women.

Methods: This was a self-controlled study carried out on 79 second-year female medical students in the Department of Physiology, King Faisal University, Dammam, Saudi Arabia during the year 2007. The students were assessed before, and after they were subjected to a mental (exam), and 2 physical stressors. Measurements of PPT and PTOL were carried out using a pressure algometer. The 2 physical stressors used were: cold water immersion and isometric exercise (ISO EX) with a dynamometer. Students' body mass indices were measured in addition to the measurement of blood pressure and heart rate for each student before, and after exposure to the stressors.

Results: All 3 stressors significantly increased the PPT values (p=0.000). The PTOL was also significantly increased immediately after exposure to the physical stressors (p=0.000), while for the mental stressor, the PTOL readings were not significantly increased. Among the 3 types of stressors, the cold water immersion was the most effective in increasing PPT and PTOL. Moreover, a significant (p=0.009) negative correlation was demonstrated between the BMI and PTOL readings.

Conclusion: Various types of physical and mental stressors significantly increased PPT and PTOL readings in young female adults, in addition to the significant findings that students with higher body mass indices tolerated pain less.

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Pain sensation with its neurophysiologic mechanisms of mediation and modulation has been extensively studied in animals. Stress-induced analgesia (SIA) was one of these mechanisms to be addressed with experimental stressors being inflicted upon the study subjects. Studies of pain in humans where natural stressors exist are few, due to the difficulty of implementing such a study, and the multifold challenges to pain scoring in humans. Pain is a multidimensional (sensory, emotional, and cognitive) experience unique to the individual, and its scores are affected by a person's past experience with pain.[1,2] High reliability is required for pain measurement, which means multiple measures at variable times. Pain scoring methods are diverse, complicating comparison of results with others, in addition to the ethical issues, which restricts the type of interventions in pain studies. Many factors influence pain including age, gender, hormones, body mass index (BMI) and ethnicity.[3-7] In studying the role of stress as a natural stimulus. Activating intrinsic pain suppressive mechanisms of the brain, one expects to learn more on how these mechanisms operate. This is expected to have an impact on pain control in postoperative, and terminal illness pain patients. A large number of studies investigated the anatomy and pharmacology of nociceptive modulating systems.[8,9] However, very little is known on the circumstances that trigger these systems. A useful approach to study intrinsic nociceptive modulating systems is by investigating the type of environmental stimuli that induce them. This is the essence of the SIA studies.[10,11] Variation in the nature of stressors used made collation of these results difficult, for example, in rodents, the exposure to intermittent cold-water swim (2oC, 10-second swims, and 10-second rests over 3 minutes) induced opioid analgesia, while the exposure to continuous cold-water swim (2oC for 3.5 minutes) induced nonopioid analgesia.[12] Moreover, Fanselow[13] reported that changing pain intensity, frequency, or body parts to which pain is directed, led to different types of analgesia. In addition, subjects' demographic variations such as age, gender, and ethnicity led to lack of consistency between different pain studies. The primary objective of this investigation was to examine the effect of various types of stressors on pressure pain threshold (PPT) and pressure pain tolerance (PTOL) values in young women and to compare these different types on their ability to affect PPT and PTOL values. A third purpose was to study how BMI correlated with PPT and PTOL values. Furthermore, by using a homogenous group of second-year female medical students, issues related to subject and stressor variations were minimized.

Methods. Ethical approval was obtained from the University's Ethical Committee, and a self-controlled trial, in which subjects were assessed before and after an intervention was used. A pilot study was previously conducted on 10 female adults to become familiar with the instrument, procedure, and normal values. Each subject acted as her own control. The study was carried out at the Departments of Physiology and Anatomy, College of Medicine, King Faisal University, Dammam, Kingdom of Saudi Arabia during the months of January to March 2007. The outcome variables were the PPT, PTOL, heart rate (HR), systolic and diastolic blood pressures (BP), before and after intervention with physical and mental stressors. All second-year female medical students at King Faisal University were requested to participate in the study. After explanation of the experimental procedure, 80 students consented. However, one was excluded due to pregnancy, reducing the total subjects included to 79. Prior to participation, subjects were questioned to ensure absence of disease conditions that could interfere, or be aggravated by the study. Subjects with peripheral neuropathy, central nervous system disturbances, and those with history of trauma, surgery to the dominant hand, or caffeine consumption 8 hours prior to the experiment were excluded from participating in the study. In addition, known cases of collagen vascular disease or Reynaud's syndrome were also excluded from the study as a precaution, as the cold water immersion test could aggravate their condition. As mentioned earlier, pregnant ladies were also excluded from the study. The PPT and PTOL were measured using a pressure algometer (Somedic, Hörby, Sweden) before, and immediately after employing the stressors. Heart rate (HR) was measured using a stop watch, and systolic and diastolic blood pressure (BP) were measured using a mercury sphygmomanometer (Riester, Stuttgart, Germany) before, and 2 minutes after employing the stressors. Three stressors were used: 2 physical stressors in the form of cold water immersion test, and an isometric exercise (ISO EX) using a handheld dynamometer. The third stressor was mental in the form of an objective structured practical exam (OSPE) in the subject of Anatomy. Between each intervention and the next one, a period of 3 weeks was given to the students to rest, and to prevent the effect of counter irritation phenomenon, where one painful intervention reduces the pain caused by a second intervention.[14] Due to logistic reasons, a measurement of baseline PPT and PTOL before the anatomy OSPE stressor was not possible. Therefore, the mean of the baselines for the ISO EX and the cold water immersion stressors was used. Each measurement was carried out twice, and a mean of the 2 values was used in further statistical analysis.

Pressure algometer. A pressure algometer (Somedic, Hörby, Sweden) was used to test the sensitivity of

stimuli applied to the ventral side of the distal phalanx of the index finger of the dominant hand. The PPT was defined as the amount of pressure (in kilopascal [kPa]) that the subject first perceived to be painful.[15] The pressure algometer probe had a diameter of 2 cm, and the pressure was increased steadily at a rate of 30 kPa/sec.[16] The subjects were instructed in the application of the algometer, and were given a chance to practice using the device. Subjects were asked to say 'pain' immediately when a discernible sensation of pain, distinct from pressure or discomfort, was felt. At this point, the algometer digital display reading for the applied pressure was recorded as PPT. The PTOL was defined as the pressure producing the maximum amount of pain that the subjects were willing, or able to accept. The PTOL was measured in the same way as the PPT, except that the subjects pushed a button to stop the pressure stimulation when they really could not tolerate any further stimulation, and the value on the digital display was recorded as the PTOL. A mean value of the 2 measurements was used for further statistical analysis. Good reliability and validity of algometric measurements in asymptomatic subjects have been previously reported.[17]

Cold water immersion test. The participant's dominant hand was immersed to a level of 5 cm above the wrist, in a mixture of crushed ice and water for 2 minutes. The ice-water temperature was maintained at 1-3^{0}C by mixing the ice-water, and controlled by a thermostat. The procedure was explained to the subjects, and they were reassured that no tissue damage is expected to occur at this level of exposure.

Isometric exercise (ISO EX). The participant's dominant hand held a strain gauge dynamometer with immovable handles. Initially, each participant was asked to make a transient maximal voluntary contraction (MVC) to determine their maximal values. Then, they were asked to hold the dynamometer for 3 minutes at one-third of their MVC, determined previously. The force developed was shown to the participant on a computer screen to which the dynamometer, a PowerLab 8SP Port (AD Instruments, Bella Vista, NSW, Australia), and a bridge amplifier were connected.

Mental stressor. The mental stressor consisted of an Anatomy exam (OSPE) in which the students had to go through 20 stations, each station lasting 2 minutes. In-between stations, a bell rang and students had to immediately move to the next station. The PPT and PTOL were measured at station number 10. The course was General Anatomy (MBAT 202) for second year. The stations involved identification of various anatomic specimens of different parts of the body. This exam amounted to 10% of their total grades for the subject of Anatomy.

Statistical analysis. The Statistical Package for Social Sciences version 11.5 (SPSS Inc., Chicago, IL., USA) was used. Descriptive statistics were used to calculate the means ± standard error of the means (SEM). Post-stressor PPT and PTOL values were compared to their baseline using paired student's t test. The same test was used to compare pre- and post BP and HR values. Pearson correlation coefficient was calculated to determine correlation between BMI and PPT and PTOL. A p-value of <0.05 was considered significant.

Results. The mean age ± SD of the participants was 19.14 ± 0.5 years (range 18-20 years), and the mean BMI ± SD of the participants was 22.84 ± 5.33 kg/m^2.

Effect of stressors on PPT. The baseline PPT values ranged between 72 and 310 kPa (n=79). The mean PPT ± SEM before using the cold water immersion stressor was 200 ± 6.32 kPa, and after the stressor, it was significantly increased to 275 ± 8.25 kPa, (37%, p=0.000). After using the ISO EX stressor, the mean PPT ± SEM of the subjects significantly increased from 167 ± 4.86 kPa to 196 ± 6.07 kPa, (17%, p=0.000). The mean PPT ± SEM of the subjects before being stressed by the Anatomy OSPE was 184 ± 4.77 kPa, and after the stressor, it significantly increased to 230 ± 7.23 kPa, (25%, p=0.000).

Effect of stressors on pressure pain tolerance. The baseline PTOL values ranged between 149 and 858 kPa (n=79). The mean PTOL ± SEM of the subjects before being stressed by the cold water immersion was 459 ± 14.44 kPa, and after the stressor, it was significantly increased to 555 ± 16.45 kPa, (21%, p=0.000). After using the ISO EX stressor, the mean PTOL ± SEM of the subjects significantly increased from 414 ± 12.82 kPa to 477 ± 17.15 kPa, (15%, p=0.000). After using the Anatomy OSPE stressor, the mean PTOL ± SEM of the subjects non-significantly increased from 437 ± 12.70 kPa to 442 ± 12.82 kPa, (0.01%, p=0.576).

Effect of stressors on HR, systolic, and diastolic BP. The HR showed a significant increase, 2 minutes after exposure to ISO EX (p=0.014), while the change was not significant after cold water immersion (p=0.095). The systolic BP showed a significant increase, 2 minutes after exposure to both ISO EX (p=0.000) and cold water immersion (p=0.001), while the increase in the diastolic BP was not significant, 2 minutes after exposure to both ISO EX (p=0.860) and cold water immersion (p=0.752). The HR and BP values, before and after the exposure to ISO EX and cold water immersion are shown in **Table 1**.

Correlation between BMI and PPT and PTOL. Five students refused to measure their weight. Therefore, 74 students participated in this part of the study. Bivariate correlation test was used. There was a significant negative

Table 1 - Mean ± SEM of heart rate (beats/minute), systolic and diastolic blood pressures (BP, mm Hg) before, and after exposure to 2 stressors (N=79).

Variable	Isometric exercise mean ± SEM		Cold water immersion mean ± SEM	
	Pretest	Post test	Pretest	Post test
Heart rate	78 ± 1.00	82 ± 1.48*	82 ± 1.41	84 ± 1.21
Systolic BP	114 ± 1.11	120 ± 1.29†	106 ± 0.89	109 ± 0.87‡
Diastolic BP	74 ± 0.76	74 ± 0.69	68 ± 0.68	69 ± 0.88

Asterisks denote levels of significance as follows: *p=0.014, †p=0.000, ‡p=0.001.

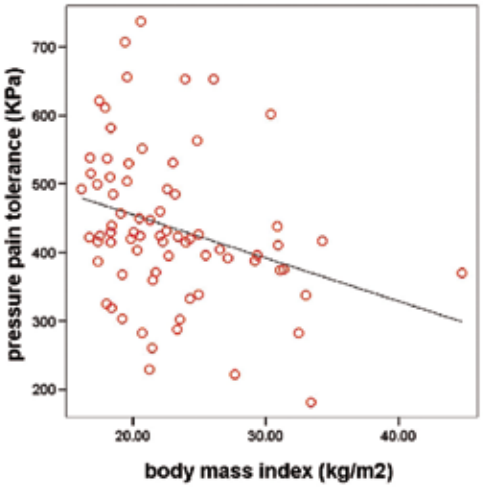

Figure 1 - Correlation between body mass index, and pressure pain tolerance, p=0.009. Data are percentages of changes from baseline values.

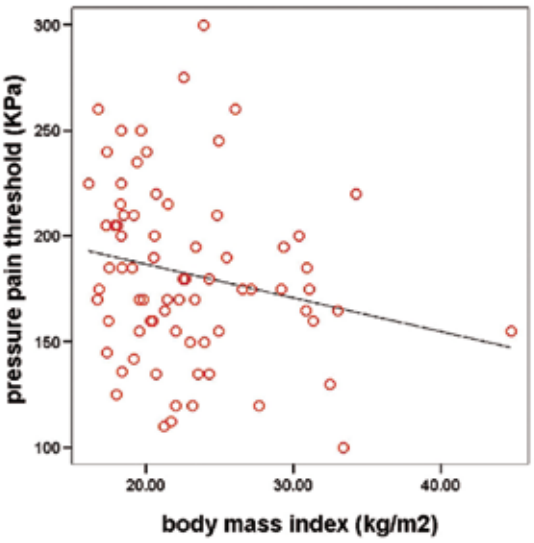

Figure 2 - Correlation between body mass index, and pressure pain threshold, p=0.081. Data are percentages of changes from baseline values.

correlation between the mean values of PTOL and the BMI (p=0.009) (**Figure 1**), which indicates that subjects with higher body mass indices tolerated pain less, while there was a non-significant negative correlation between the mean values of PPT and the BMI (p=0.081) (**Figure 2**).

Discussion. Cold water immersion has been used as a stressor in pain research, as well as in other fields such as, autonomic function testing and colonic motility.[3,18,19] Only a limited amount of research has been conducted examining alteration in pain perception following cold water immersion in humans,[3] in contrast to much more literature in this model of analgesic activation in animals.[20,21] The results from this study add to the limited database in the effect of cold water immersion on pain perception in humans. It is in agreement with the results from Washington et al's[3] study, which reported that following cold water immersion stressor, pain thresholds increased up to 100%. This increase was transient, and thresholds returned to baseline within one hour. Water temperature in pain studies using this technique ranged from 0-5^{0}C.[3,14] It was suggested that cold water immersion below 11^{0}C can induce a temporary nerve conduction block, offering an alternative explanation to endogenous analgesia for any observed increase in pain threshold values.[22,23] However, a study carried out by Ochs and Smith[24] assessed possible alterations in the functional integrity of peripheral nerves following ice water immersion. The study revealed that after the cold water immersion task, the functional integrity of large myelinated A-beta fibers was preserved. Given that myelinated fibers are more susceptible to cold induced conduction block than unmyelinated sensory fibers,[25] this simple explanation is unlikely to account for the observed analgesic response. A contradicting study carried out by Suarez-Roca et al[26] observed hyperalgesia in rats after repeated swim stress. However, this hyperalgesia can be attributed to the fact that repeated exposure to stressors leads to the release of endogenous opioids, resulting in over-activation and desensitization of opioid receptors (tolerance). Tolerance to the analgesic effects of opioids is associated with hyperalgesia,[27,28] and is related to increased activity of N-methyl-D-aspartate receptors.[29] In the present study, PPT increased up to 37% after cold water immersion compared to a 100% increase in Washington et al's[3] study. The difference in the percentage of change between the 2 studies might be attributed to the difference in pain induction methods (electrical and thermal stimuli versus pressure stimulus). The present study used cold water immersion of the hand, to provide a stressor in order to activate endogenous analgesic systems. Thus, the findings that the cold water immersion task is

capable of inducing an endogenous analgesic response in healthy young females, further lends weight to the suggestion of earlier investigators. A rise in HR and BP after cold water immersion test is explained on the basis of rising plasma epinephrine and norepinephrine (NE) during the test.[30]

Few studies were conducted to examine the impact of ISO EX on pain perception. In the present study, short duration (namely, 3 minutes), low intensity (namely, 30% MVC) ISO EX using a dynamometer significantly increased the PPT and PTOL values. The results from the present study are in agreement with previous studies.[31-33] However, several investigators have reported lack of analgesia during ISO EX.[34,35] Kosek and Ekholm[31] reported that after the performance of submaximal ISO EX by 14 women, the PPTs were significantly elevated at the start of the exercise and for 5 minutes following exercise. In addition, Koltyn et al[32] reported that exposure to submaximal ISO EX produced a significant increase in pressure PPT in 16 healthy women. Furthermore, Staud et al[33] reported significant elevations in PPTs after ISO EX in both forearms in healthy women compared to women with fibromyalgia. However, Feine et al[34] found that there were no significant alterations in pain thresholds to heat stimuli applied to each forearm during ISO EX and isotonic exercise in a mixed sample of men and women. Consequently, it is possible that the sample of the present study was more homogenous compared to the previous study sample. In addition, differences in methodology between Feine et al's[34] study and the present study include the exercise stimulus (mode, intensity and duration), and pain induction method (thermal stimulus versus pressure stimulus), while in Koltyn et al's[32] study, the exercise stimulus and the pain induction method were similar to the present study, thus the results were similar. Heng et al[36] showed that during ISO EX and isotonic exercise, systolic BP increased in 12 healthy subjects. In addition, van Rooyen et al[37] showed that systolic and diastolic BPs, and mean arterial pressure increased in 2 different groups after exposure to an acute laboratory stressor, hand dynamometer exercise. In the present study, there was a significant increase in the HR (p=0.014), as well as in systolic BP (p=0.000), but not in diastolic BP after ISO EX.

When exercise becomes painful, nociceptive information transmitted from skeletal muscles to the brain via Type III and IV nerve fibers can result in the initiation of descending pain modulation. In addition, stimulation of Type III and IV nerve fibers is essential for some pituitary hormonal responses (adrenocorticotropic hormone and beta-endorphin), and changes in plasma catecholamines have been found in response to ISO EX, when relative intensity is above 20% MVC.[38] Kjaer et al[38] reported that plasma beta-endorphin levels were elevated following ISO EX. Research has indicated that both beta-beta-endorphin and catecholamines play a role in pain regulating systems.[39] Thus, it is possible that alterations in pain perception following ISO EX were potentially explained by increases in beta-endorphin and/or catecholamines levels associated with stimulation of Type III and IV afferent fibers by ISO EX.

In the present study, the mental stressor in the form of OSPE in the subject of Anatomy significantly increased the PPT, but not the PTOL. This might be attributed to the fact that this Anatomy OSPE exam amounted to only 10% of the students' total grade (it was not an adequate mental stressor). Michelotti et al[40] studied the effects of a natural emotional stressor (an academic examination) on PPTs of the masticatory muscles of 16 gender-matched students. In stressed students, the PPTs of the masticatory muscles were significantly lower on the day of examination, and on the days nearest the exam. No significant change was found in beta-beta-endorphin plasma levels. However, Paran et al[41] reported that mental and physical stressors significantly increased epinephrine and NE levels compared to rest. The increase was progressive from mental stress, through ISO EX to the treadmill test. A study carried out by Willer et al[42] reported that the cumulative effects of repetitive stress induced by anticipation of pain (a form of mental stress), increased the threshold of nociceptive flexion reflex of the lower limb in healthy volunteers. On the other hand, and in response to a different mental stressor, Mechlin et al[7] showed no evidence for SIA in 2 different ethnic groups of volunteers. The mental stress was a modified version of a test called Trier Social Stress Test (TSST), where serial addition was included as opposed to serial subtraction. The inability to detect any evidence for SIA may be related to the time course of events since pain testing occurred 10 minutes after the cessation of stressors leading to the recovery of cardiovascular and neuroendocrine levels preventing the detection of SIA.

Some laboratory studies in humans have attributed SIA to mental and physical stressors,[43,44] others have found it in only subgroups of individuals,[45] and at least one study found that participants were more sensitive to pain following stress testing.[46]

In the present study, a significant negative correlation was demonstrated between the BMI and PTOL readings. This finding was previously unknown, and future research regarding the relation between BMI and PTOL is recommended. The PPT also exhibited a similar pattern as PTOL, but it did not reach the level of significance. A study carried out by

Pradalier et al[6] documented that there is a significant negative correlation between the degree of overweight and the threshold of the nociceptive reflex in humans. The hypothesis of an abnormality of the endogenous morphine-like system, or of its control in human obesity was suggested. Another study by Larsson and Mattsson[47] reported that obese women perceived disability to a much higher extent ($p<0.003$) than did the normal weight women. The main problems concerned walking outdoors or on stairs, and moderate housework requiring squatting, stooping, or lifting. However, a number of studies found out that subjects with high body mass indices have higher pain threshold readings than those of other categories so they feel less pain.[48-50] A hypothesis is suggested that the diminution of the susceptibility to pain in obese subjects could be due to the increase in endogenous opiate activity. Additional research is needed to clarify whether PPT and PTOL are negatively or positively correlated with BMI.

There are a few limitations regarding the interpretation of findings from this study. First, it is possible that results from this study may have been influenced by behavioral artefacts (suggestions or expectations). However, to minimize potential behavioral artefacts, conversations between the participant and the investigator were kept to a minimum, so that the participants were not given clues indicating the hypothesis of this study. Second, since all subjects were females, PPT and PTOL values may have been influenced by hormonal effect of the ovulatory cycle. However, this effect was minimized by taking the pre- and post stressor data on the same session. In addition, there are studies indicating that the influence of the ovulatory cycle on pain perception is minimal.[51] A third limitation was the assumption that the increase in PPT and PTOL after cold water immersion stressor was either due to an increase in peak stimulus, or a non-documented decrease in basal body temperature.[52]

This study concluded that physical and mental stressors significantly increase PPT and PTOL readings in young women. The best response was achieved with cold water immersion stressor. The Anatomy OSPE only significantly increased the PPT but not the PTOL. In addition, there is a significant negative correlation between BMI and PTOL readings. Further research is needed, examining the mechanisms responsible for cold water immersion and mental stressors induced analgesia. Research regarding the relation between BMI and pain threshold and tolerance is recommended.

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Related topics

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