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ORIGINAL ARTICLE

The role of 5-HT3 receptor inhibition in human pain modulation: a double-blind crossover study

O papel da inibição do receptor 5-HT3 na modulação da dor humana: um estudo duplo-cego cruzado

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ABSTRACT

BACKGROUND AND OBJECTIVES: Dysregulation of descending pain modulation, characterized by an imbalance between facilitator and inhibitory pathways, plays a key role in the development and persistence of chronic pain. The conditioned pain modulation (CPM) paradigm is a well-established method for assessing descending pain control in humans. The 5-HT3 receptor (5-HT3R) is implicated in descending pain facilitation and has been associated with persistent pain states. This double-blind, crossover physiological study aimed to investigate the effects of 5-HT3R inhibition with ondansetron on thermal and mechanical pain thresholds, assessed via quantitative sensory testing (QST), and on CPM (thermal stimulus) in healthy adults.

METHODS: Seventeen healthy volunteers underwent quantitative sensory testing (QST) and conditioned pain modulation (CPM) assessments at baseline and following an intravenous infusion of either 8 mg ondansetron or saline (NaCl 0.9%). One week later, they were reassessed using the opposite treatment following the same protocol. Changes in QST and CPM before and after each intervention were analyzed using paired t-tests or Wilcoxon matched-pairs signed-rank tests (significance threshold: $p<0.05$).

RESULTS: Ondansetron had no significant effect on QST measures, but significantly enhanced CPM compared to saline.

CONCLUSION: These findings suggest that 5-HT3R inhibition enhances endogenous pain inhibition without altering acute pain thresholds, highlighting its potential role in central pain modulation.

KEYWORDS: Serotonin 5-HT3 receptor antagonists, Pain, Ondansetron, Central nervous system sensitization.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A desregulação da modulação descendente da dor, caracterizada por um desequilíbrio entre as vias facilitatórias e inibitórias, desempenha um papel fundamental no desenvolvimento e na persistência da dor crônica. O paradigma da modulação condicionada da dor (CPM - conditioned pain modulation) é um método bem estabelecido para avaliar o controle descendente da dor em humanos. O receptor 5-HT3 (5-HT3R) está relacionado com a facilitação descendente da dor e tem sido associado a estados de dor persistente. Este estudo fisiológico duplo-cego e cruzado teve como objetivo investigar os efeitos da inibição do 5-HT3R com ondansetrona nos limiares térmicos e mecânicos de dor, avaliados por meio de teste sensitivo quantitativo (QST - quantitative sensory testing), e no CPM (estímulo térmico) em adultos saudáveis.

MÉTODOS: Dezessete voluntários saudáveis foram submetidos a avaliações de QST e CPM no início do estudo e após receberem uma infusão de 8 mg de ondansetrona ou solução salina (NaCl 0,9%) endovenosas. Uma semana depois, eles foram reavaliados usando o tratamento oposto seguindo o mesmo protocolo. As alterações no QST e na CPM antes e depois de cada intervenção foram analisadas por meio de testes t pareados ou testes de Wilcoxon (limiar de significância: $p<0,05$).

RESULTADOS: A ondansetrona não apresentou efeito significativo nas medidas do QST, mas aumentou significativamente o CPM em comparação com a solução salina.

CONCLUSÃO: Esses achados sugerem que a inibição do 5-HT3R aumenta a inibição endógena da dor sem alterar os limiares de dor aguda, destacando seu papel potencial na modulação central da dor.

DESCRITORES: Antagonistas do receptor de serotonina 5-HT3, Dor, Ondansetrona, Sensibilização do sistema nervoso central.

HIGHLIGHTS

- This double-blind, crossover physiological study aimed to investigate the effects of 5-HT3R inhibition with ondansetron on thermal and mechanical pain thresholds, assessed by quantitative sensory testing (QST), and on conditioned pain modulation (CPM) in healthy adults
- In this study, ondansetron had no significant effect on QST measurements, but significantly increased CPM compared to saline solution (0.9% NaCl)
- These findings suggest that 5-HT3R antagonism by ondansetron increases endogenous pain inhibition without altering acute pain thresholds, highlighting its potential role in central pain modulation

INTRODUCTION

Dysregulation of descending pain modulation, characterized by an imbalance between facilitator and inhibitory pathways, plays a pivotal role in the pathogenesis and persistence of chronic pain[1]. Thus, restoring central pain processing represents a promising therapeutic strategy for improving patient outcomes[2-4].

A comprehensive understanding of the molecular mechanisms underlying pain transmission and modulation in the nervous system is crucial for advancing treatment options for patients with chronic pain. Such knowledge may enable the development of targeted interventions to address the significant plasticity observed in facilitator and modulatory systems in these individuals[5].

Descending pathways are not exclusively inhibitory; they can also facilitate pain[6]. For example, serotonergic pathways exert both inhibitory and facilitator effects on nociceptive processing in the spinal cord[7]. These responses depend on the specific 5-HT receptors activated, their distribution in the nervous system, and whether the pain condition is acute or chronic[7,8].

Among the 5-HT receptor subtypes, the 5-HT_3 receptor (5-HT_3R) has attracted particular attention. Studies highlight its prominent role in the descending facilitators pain system and its involvement in various persistent pain conditions, including inflammatory pain, postoperative pain, visceral hypersensitivity, neuropathic pain, cancer pain, and opioid-induced hyperalgesia[8]. Ondansetron, a highly selective 5-HT_3R antagonist commonly used as an antiemetic for surgical and chemotherapy patients, has shown analgesic effects in animal models[9,10].

The conditioned pain modulation (CPM) paradigm is a widely used method for assessing descending pain modulation in humans[11]. CPM is a psychophysical test based on the concept of "pain inhibiting pain", in which the intensity of a painful test stimulus is reduced during or immediately after the application of a conditioning stimulus.

Recently, research has focused on evaluating the reliability of CPM. While CPM has been shown to be a reliable measure, its reliability is strongly influenced by the stimulation parameters and methodological choices, which should be carefully considered by investigators[12,13]. The magnitude of this reduction in pain perception is referred to as the CPM effect[11]. Studies have demonstrated that CPM is less effective in patients with neuropathic pain from various etiologies[2,14-16].

The present authors' hypotheses is that inhibiting 5-HT_3R with ondansetron would enhance the descending pain modulation system by improving CPM in healthy volunteers. To test this hypothesis, a physiological intervention study was conducted using a blinded crossover design in which sensitivity and CPM were assessed before and after ondansetron or saline administration in humans.

METHODS

Experimental procedures

A randomized, double-blinded crossover study that was approved by the Institutional Review Board (Protocol Number: 56649116.0.0000.5259). All experiments were conducted following the Declaration of Helsinki and written informed consent was obtained from all subjects. The clinical trial was registered with The Brazilian Registry of Clinical Trials – ReBEC (U1111-1232-3630)[17].

Volunteers characteristics

Seventeen healthy individuals of both genders, aged between 18 and 40, participated in the study (convenience sample). The research was conducted in the sensitivity assessment laboratory of the pain clinic at the Pedro Ernesto University Hospital - Rio de Janeiro State University.

To mitigate possible thermal influences on the tests, the room temperature was maintained at 22 °C and all evaluation conditions were standardized. Exclusion criteria included chronic diseases or the use of analgesics, antidepressants, benzodiazepines, or any other psychoactive drug within the 14 days preceding the tests. Demographic characteristics recorded included sex (female and male), age (years), body mass index (BMI = body mass divided by the square of the body height), and self-declared race (white and non-white).

Quantitative sensory test (QST)

Thermal sensitivity was assessed following familiarization and demonstration[18]. The study used a thermal testing equipment *(*Medoc TSA-2001; Medoc, Israel*)*, which employed a Peltier device with an active surface of 30×30 mm. The intensity of the stimulus was gradually increased or decreased from a baseline of 32 °C (1 °C/s, cohort limits: 0 °C and 50 °C) until the subject pressed a response button, registering the temperature and returning it to baseline. Tests were conducted on the non-dominant anterior antebrachial area. The researchers evaluated warm and cold detection thresholds (four stimuli each), as well as heat and cold pain thresholds (three stimuli each), with the mean values used for analysis.

Cold detection threshold (CDT) and warm detection threshold (WDT)

Volunteers were instructed to press the stop button when they perceived a change in the skin temperature to cooler (CDT) and to warm (WDT). The mean of four stimuli was used as CDT and WDT.

Cold pain threshold (CPT) and heat pain threshold (HPT)

Volunteers were instructed to press the stop button when they perceived a change in the skin temperature from a cold sensation to a burning, stinging, drilling, or aching sensation (CPT) and from warm to burning, stinging, drilling, or aching sensation (HPT). The mean of three stimuli was used as CPT and HPT.

Pressure pain threshold (PTT)

PPT or peak pressure (PP) was measured with a manual pressure algometer (Medoc Algometer, Medoc Ltd., Ramat Yishai, Israel,

2021) using a probe with a circular surface of 1 cm^2. Pressure pain was evaluated in the same area where the thermal sensory test was conducted. Pressure was applied perpendicularly against the skin at a rate of 50 kPa/s, and the participants were instructed to press a button when the sensation of pressure changed to a burning, stinging, drilling, or aching sensation. The mean of three stimuli was considered as the pressure pain threshold.

Conditioned pain modulation (CPM)

CPM was calculated as the difference in pain rating, using a 0 to 100 numerical pain scale (NPS), between two identical nociceptive test stimuli induced before, at baseline, and parallel to a conditioned remote nociceptive stimulus. The test stimulus was a 30x30 mm contact heat stimulus (TSA-2001, Medoc, Israel) applied on the non-dominant anterior antebrachial area. The intensity of the test stimulus was individually predetermined, based on the psychophysical parameter of a pain score of 60, which was the thermal stimulus that induced a painful sensation of 60 on the NPS. After 15 minutes, the contralateral hand was immersed in a basin with hot water at a temperature of 46.5 °C (Cooling bath, Carci, Brazil) for 60 seconds (conditioned nociceptive stimulus), and, during the last 30 seconds, the test stimulus was repeated. Participants were again asked to score the intensity of the pain. CPM was determined as the difference between the second and first values for pain intensity after the two stimuli. Thus, a CPM value lower or more negative was considered a more efficient CPM.

Randomization

Randomization was conducted by a medical doctor not involved in the project, using a sealed envelope that specified the treatment infusion for the first week-either ondansetron or isotonic saline solution (NaCl 0.9%). The doctor prepared the solution and provided it to the researcher. Neither the volunteer nor the researcher knew which solution was administered. The identification of the solution administered to each volunteer was only revealed at the end of the study.

Treatments

Ondansetron: A 5-HT_3R antagonist, ondansetron (8 mg in 20 mL of saline)[19], was administered intravenously over 15 minutes. A baseline electrocardiogram was performed on all participants to ensure a normal QTc interval.

Control (isotonic saline solution): NaCl 0.9% (20 mL) was administered intravenously over 15 minutes.

Experimental design (Figure 1)

The tests were performed in four periods:

Period 1: Measurements of CPT, WPT, CPT, HPT, and CPM were performed 10 minutes after the intravenous catheter was inserted (Baseline);

Period 2: Immediately after period 1 and randomization, volunteers received an intravenous injection of either 8 mg ondansetron in 20 mL of saline (Ondansetron) or 20 mL saline (Saline). CPT, WPT, CPT, HPT, and CPM measurements were repeated 30 minutes after the solution was administered;

Period 3: One week later, CPT, WPT, CPT, HPT, and CPM were measured 10 min after the intravenous catheter was inserted (Baseline);

Period 4: Immediately after period 3, volunteers received the opposite solution to what they received the previous week. Each participant thus received both solutions, serving as their control (crossover), resulting in 34 experiments. CPT, WPT,

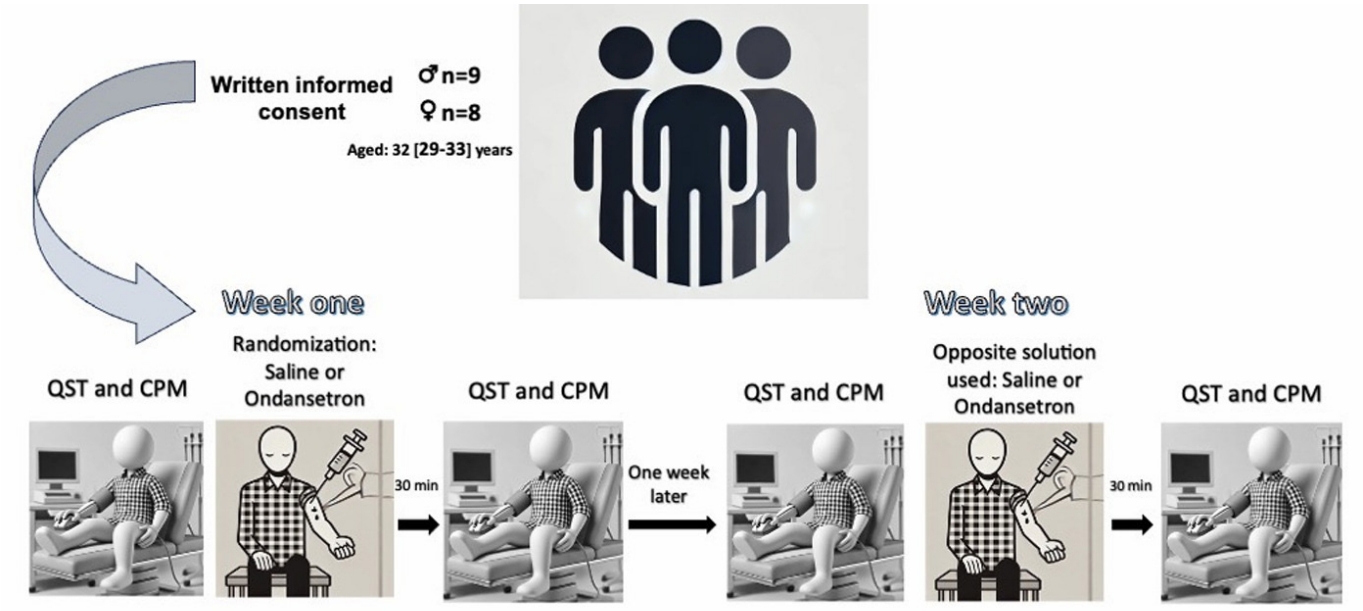

Figure 1. Schematic of the experimental design.

CPT, HPT, and CPM measurements were repeated 30 minutes after administering the solution.

To enhance reliability, comparisons were conducted within each session, with baseline analysis performed before administering each solution[20].

After randomization, seventeen healthy volunteers were subjected to quantitative sensory testing (QST) and conditioned pain modulation (CPM) exams during the first week, both before and after the infusion of Saline or Ondansetron. One week later, the same volunteers underwent QST and CPM exams again, before and after receiving the opposite solution from the first week. The study was double-blind.

Statistical analysis

Data are presented as mean (SD), median [IQR], or proportion. The Shapiro-Wilk test was used to assess data normality. Changes in CDT, WDT, CPT, HPT, PP, and CPM were calculated at baseline and after infusion of the studied solutions (ondansetron or saline). CPM was expressed as a percentage change from baseline. Differences between conditions were analyzed using paired t-tests for normally distributed data or Wilcoxon matched-pairs signed-rank tests for non-normally distributed data. Statistical analyses were conducted using STATA 18, with $p<0.05$ considered statistically significant.

RESULTS

Characteristics of the volunteers

Table 1 summarizes the characteristics of the volunteer. A total of seventeen participants were included in the study, with nine (52.9%) being male. The median age of the volunteers was 32 [29-33] years, and the mean (SD) BMI was 25.2 (±3.0) Kg/m^2. No patients were removed from the study.

All patients were followed until the conclusion of the study. There were no adverse effects related to the drug or the tests employed.

Effects of 5-HT3 serotoninergic receptor inhibition on pain sensitivity and conditioned pain modulation (CPM)

Table 2 and Figure 2 illustrate the pain sensitivity and CPM results before (baseline) and after the ondansetron or saline administrations.

Thermal detection and pain intensity

No significant differences were observed in the changes in CDT, WDT, CPT, HPT, and PTT before and after the infusion of either saline or ondansetron.

Conditioned pain modulation (CPM)

Ondansetron significantly improved CPM, whereas saline did not. The change in CPM, evaluated as a ratio relative to baseline, was greater after ondansetron infusion (91.6% [83.3%-106.2%]) compared to saline infusion (104.5% [92.8%-111.1%]), with a p-value of 0.013.

CPM values are presented as ratios relative to baseline values. Seventeen volunteers (n=17) underwent a CPM exam at baseline. After randomization, they received an injection of either saline or ondansetron, followed by another CPM exam. One week later, the same volunteers underwent the CPM exam again at baseline and after receiving the opposite solution from the previous week (a crossover study).

DISCUSSION

The study demonstrated that inhibition of 5-HT$_3$R with ondansetron enhanced conditioned pain modulation (CPM) without affecting thermal detection thresholds, thermal pain thresholds, or pressure pain thresholds. These findings suggest a potential therapeutic role for 5-HT$_3$R inhibition in restoring central pain processing. To the knowledge of the present authors, this is the first study to show that 5-HT$_3$R inhibition can improve CPM in humans.

The 5-HT$_3$ receptor is widely distributed across both the peripheral and central nervous systems. Unlike other 5-HT receptor subtypes, which are G-protein-coupled, 5-HT$_3$R is a ligand-gated ion channel that, upon activation, induces rapid neuronal depolarization[21]. This receptor has been identified in several key regions, including the area postrema, nucleus of the solitary tract, dorsal motor nucleus of the vagus, caudate nucleus, nucleus accumbens, amygdala, hippocampus, entorhinal cortex, frontal cortex, cingulate cortex, and the dorsal horn of the spinal cord. These regions are critically involved in regulating the vomiting reflex, pain processing, reward mechanisms, and anxiety control[22]. In the spinal cord, 5-HT$_3$R is especially concentrated in the superficial layers of the dorsal horn, where it mediates excitatory pathways from the brainstem and modulates spinal excitability through its effects on spinal neurons[23].

The findings indicate that 5-HT$_3$R inhibition did not alter pain sensitivity to thermal or pressure stimuli, which aligns with prior evidence of the receptor's limited role in acute pain modulation. For instance, co-administration of ondansetron with paracetamol did not enhance analgesia in patients undergoing abdominal surgery[24]. Conversely, a recent study found that ondansetron reduced early postoperative pain following appendectomy. Additionally,

Table 1. Demographic and clinical characteristics of study volunteers.

Characteristics	Total (n=17)
Gender, n(%)	
Male	9 (52.9%)
Female	8 (47.1%)
Age (years), median [IQR]	32 [29-33]
Body mass index (kg/m^2), mean(SD)	25.2 (±3.0)
Ethnicity, n(%)	
White	6 (35.3%)
Non white	11(64.7%)

Table 2. Quantitative sensory testing of voluntaries during the experimental period.

Stimulus	Saline	Ondansetron	p-value
Warm detection threshold (°C)			
Baseline (M1)	35.12 (1.77)	35.14 (1.07)	
After treatment (M2)	35.45 (1.27)	36.06 (2.14)	
Difference (M2-M1)	-0.06 (2.46)	-0.76 (1.61)	0.316
Cold detection threshold (°C)			
Baseline (M1)	28.59 (3.13)	29.97 (1.47)	
After treatment (M2)	28.57 (1.86)	29.20 (2.67)	
Difference (M2-M1)	-0.01 (2.46)	-0.76 (1.61)	0.361
Heat Pain Threshold (°C)			
Baseline (M1)	45.43 (2.30)	46.42(2.79)	
After treatment (M2)	46.44 (1.55)	46.62(2.25)	
Difference (M2-M1)	1.01 (2.53)	0.20(2.50)	0.310
Cold Pain Threshold (°C)			
Baseline (M1)	9.04 (5.7)	9.66(5.25)	
After treatment (M2)	11.28 (5.91)	10.25(7.16)	
Difference (M2-M1)	2.24 (6.71)	0.60 (5.42)	0.489
Pressure pain threshold (kPa)			
Baseline (M1)	294.2 [263.3-395.3]	397.1 [213.0-397.4]	
After treatment (M2)	329.4 [209-7,428.5]	302.5 [200.6- 351.5]	
Difference (M2-M1)	7.6 [-67.2- 81.6]	-4.6 [-41.8- 33.6]	0.687

Data are presented as mean (SD) or median [IQR]. n=17.

previous research[16] demonstrated that disruption of 5-HT_3R - either genetically or pharmacologically - reduced persistent, but not acute, nociception after tissue injury in mice[25]. These findings suggest that 5-HT_3R inhibition may not significantly modulate acute physiological pain, even though it has been implicated in inflammatory pain[8].

The improvement in CPM following ondansetron administration in the study suggests that 5-HT_3R may play a role in the central serotonergic facilitation of nociception. Prior studies have shown that 5-HT_3R contributes to nociceptive facilitation within the spinal cord[23,25], which is consistent with observations in humans and with animal model data. In animal studies, descending pain modulation is often assessed through the Diffuse Noxious Inhibitory Controls (DNIC) paradigm[26]. In a rat model of neuropathy induced by spinal nerve ligation, DNIC was abolished but restored following ondansetron treatment[27].

Recent investigations have highlighted the role of NK1-expressing neurons in laminae I–III of the spinal cord, which are primarily nociceptive-specific and project to the parabrachial area and brainstem. These neurons are essential for pain transmission, and evidence suggests that 5-HT_3R-mediated descending facilitation enhances central spinal pain processing, particularly in chronic pain states such as neuropathy. Lesioning NK1-expressing neurons diminishes spinal neuron responses, mimicking the effects of spinal ondansetron and those seen in animals with 5-HT_3R knockout. This supports the involvement of 5-HT_3R in modulating nociception via spinal–brainstem–spinal loops[19]. In a rat model of chemotherapy-induced neuropathy, increased 5-HT_3R expression was observed in the superficial dorsal horn (laminae I–II) via

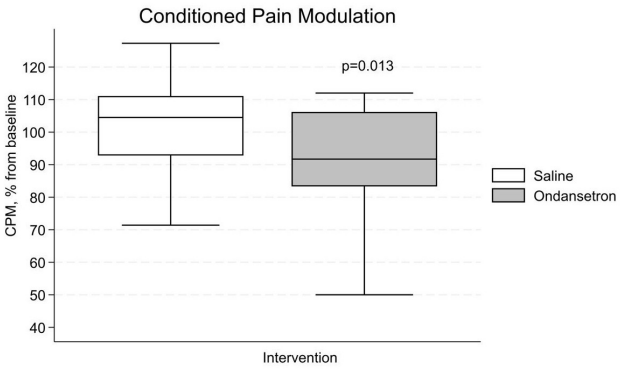

Figure 2. Effect of saline and ondansetron injections on conditioned pain modulation.

immunohistochemistry, and intrathecal ondansetron reversed cold and mechanical hyperalgesia[28]. Moreover, a single injection of ondansetron was shown to reduce pain scores for up to two hours in patients with chronic neuropathic pain[19].

Descending pathways involved in DNIC must be activated by noxious stimuli, possess widespread receptive fields, connect directly to the spinal cord, and be capable of inhibiting Wide Dynamic Range (WDR) neuron activity[29]. Although the exact mechanism of WDR inhibition remains unclear, it may involve postsynaptic inhibition, activation of spinal inhibitory circuits, or presynaptic modulation of nociceptive inputs. These features underscore the importance of an intact DNIC pathway - and by extension, CPM - for effective pain inhibition. Pharmacological

tools are often used to investigate CPM, especially in healthy individuals with presumably intact endogenous pain modulation systems. Thus, the present study's findings demonstrate that 5-HT$_3$R inhibition can enhance CPM, suggesting its potential as a therapeutic target for improving endogenous pain control[30].

A comprehensive review[31] gathered substantial evidence supporting the use of 5-HT(1A) and 5-HT(7) receptor agonists, as well as 5-HT(2A) and 5-HT(3) receptor antagonists, as promising agents for the treatment of various pain conditions[31]. Nevertheless, further research is needed to replicate the present study's findings in patients with neuropathic pain and to determine whether 5-HT$_3$R inhibition can enhance CPM and reduce pain in this population[32,33].

The present study has certain limitations that must be acknowledged. First, the relatively small sample size may affect the generalizability of the results, although it offers valuable insights into the effects of serotonergic modulation on pain perception. Second, while short-term improvements in CPM were observed, the study design did not allow to assess the duration of these effects, which may be crucial for understanding long-term therapeutic implications. Additionally, the inherently subjective nature of pain reporting - which can vary significantly across individuals - may introduce variability in the assessment of pain intensity. Despite these limitations, the present findings provide meaningful contributions to the understanding of pain modulation mechanisms and highlight directions for future research.

CONCLUSION

The study demonstrates that inhibition of 5-HT$_3$R by ondansetron in healthy adults enhances conditioned pain modulation (CPM) without altering responses to acute physiological pain, highlighting the important role these receptors may play in central pain processing. Although these findings are promising, further research is needed to confirm the results in patients with chronic pain. Future studies should also investigate the duration and sustainability of the observed effects. Nonetheless, these preliminary insights offer a valuable foundation for exploring 5-HT$_3$R antagonists as a therapeutic strategy in chronic pain management, potentially paving the way for novel interventions in pain treatment.

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