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ORIGINAL

POTENTIAL OF DEXMEDETOMIDINE IN ALLEVIATING CHRONIC VISCERAL PAIN: IMPLICATIONS FOR ENHANCED RECOVERY AND PHYSICAL PERFORMANCE THROUGH PVT1/CXCR5

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ABSTRACT

Background: Chronic visceral pain (CVP), characterized by prolonged internal organ pain, significantly impairs quality of life and limits physical activity, posing challenges for rehabilitation and sports performance. Dexmedetomidine, a selective α2-adrenergic receptor agonist, is known for its analgesic properties, yet its underlying mechanisms in alleviating CVP remain unclear. This study investigates the effects of dexmedetomidine on CVP, focusing on the PVT1/CXCR5 pathway, to understand its potential role in enhancing recovery and supporting physical function. **Methods:** Rats were divided into two groups for CVP modeling and dexmedetomidine treatment. The CVP models included blank, CVP, CVP + shNC, and CVP + shPVT1 groups, while dexmedetomidine-treated groups included W1 (control), W2 (DMSO), W3 (CVP only), and W4–W6 (CVP with low, medium, and high dexmedetomidine doses, respectively). Dexmedetomidine was administered intraperitoneally, and pain thresholds were measured using the von Frey filament test and abdominal withdrawal reflex (AWR) scores. Additional assessments included visceral motor response, mean arterial pressure, and PVT1/CXCR5 mRNA and protein expression levels analyzed via qRT-PCR and ELISA. **Results**: Dexmedetomidine alleviated CVP

in a dose-dependent manner, significantly increasing pain thresholds and reducing AWR scores compared to untreated CVP groups. It also modulated the PVT1/CXCR5 pathway, with reduced mRNA and protein expression levels of PVT1 and CXCR5 in treated groups. Lower expression of CXCR5 correlated with decreased inflammatory markers and improved recovery indicators. These findings suggest that dexmedetomidine's regulation of the PVT1/CXCR5 pathway underpins its analgesic effects, potentially facilitating better physical recovery and readiness for activity. **Conclusion**: This preclinical study highlights dexmedetomidine's ability to alleviate chronic visceral pain via modulation of the PVT1/CXCR5 pathway. By improving pain management and reducing inflammation, dexmedetomidine may contribute to enhanced physical recovery and rehabilitation outcomes, offering potential applications for athletes and individuals requiring optimal functional performance. Further research is warranted to explore its clinical implications in sports and physical activity contexts.

KEYWORDS: Chronic Visceral Pain; Dexmedetomidine; Inflammatory Factors; PVT1/CXCR5

1. INTRODUCTION

Chronic visceral pain (CVP) is a debilitating condition characterized by persistent pain originating from internal organs, significantly affecting individuals' physical and psychological well-being. It is associated with conditions such as irritable bowel syndrome and chronic pancreatitis, leading to impaired daily functioning, reduced quality of life, and increased healthcare costs. The persistent nature of CVP often limits individuals' ability to engage in physical activity, further exacerbating the risk of deconditioning, psychological distress, and social isolation. Addressing CVP is, therefore, not only a medical necessity but also critical for supporting functional recovery and promoting active lifestyles, particularly in populations that rely on physical performance for their well-being or professional activities, such as athletes. Dexmedetomidine, a selective α2-adrenergic receptor agonist, has gained attention for its potent analgesic and anti-inflammatory properties(Thibaut et al., 2020).

It has been widely used in clinical settings for sedation and pain relief. Unlike opioids, dexmedetomidine provides analgesia without significant respiratory depression, making it a safer alternative for managing chronic pain. However, its potential mechanisms in alleviating CVP remain largely unexplored(Carter et al., 2009). Recent studies suggest that molecular pathways, such as the PVT1 (Plasmacytoma Variant Translocation 1)/CXCR5 (C-X-C Chemokine Receptor Type 5) axis, may play a significant role in mediating pain and inflammatory responses. Understanding the interaction between dexmedetomidine (Grundy et al., 2019) and this pathway could

offer new insights into its therapeutic potential for CVP management(Hartmann, 2010; Long et al., 2022; Qiu; Sadeghi et al., 2018). In the context of sports and physical activity, chronic pain, including CVP, poses significant challenges. Pain not only restricts physical performance but also delays recovery and rehabilitation, creating a barrier to achieving optimal functional outcomes. Identifying effective interventions that alleviate pain while promoting anti-inflammatory effects is crucial for athletes and individuals aiming to maintain or restore physical activity levels. By modulating pathways that contribute to pain and inflammation, dexmedetomidine may provide a novel approach to enhance recovery and physical performance, bridging the gap between pain management and sports medicine.

(Cortes-Altamirano et al., 2018; Treede et al., 2019). (Nakajima et al., 2018). The α2-adrenergic receptor agonists produce analgesic and sedative effects in the central nervous system (Yu, 2012). In addition to its sedative effects, many studies have also shown that dexmedetomidine has certain analgesic properties (Guo et al., 1996; Kamibayashi et al., 2000; Kendig et al., 1991; Nelson et al., 2003).

In children undergoing surgery for congenital megacolon, ropivacaine caudal block combined with tracheal intubation under general anesthesia, dexmedetomidine administered via caudal injection has a significant synergistic effect on intraoperative, postoperative acute visceral pain and sedation inhibition. Dex can stimulate presynaptic receptors, and bind to the neurokinin-1 receptor of spinal dorsal horn neurons, thereby relieving visceral pain. Dex can promote the release of acetylcholine by cholinergic neurons to relieve visceral pain. Dex can also regulate rectal distension-related visceral pain through opioid receptors. The gut microbiota is a key regulatory factor in visceral pain by regulating the intestinal environment and modulating visceral pain through the brain-gut axis and stress systems. LncRNAs are transcripts that exceed 200 nucleotides in length and do not encode proteins (Napoli, 2021; Poree et al., 1998). For instance, the downregulation of lncRNA NONRATT021972 in DM rats reduces the release of inflammatory cytokine TNF-α, leading to decreased excitability of DRG neurons and reduced mechanical and thermal hyperalgesia (Pan et al., 2021). Another example is lncRNA MALAT1, which promotes neuropathic pain and neuro-inflammation (Liu et al., 2016).

The role of LncRNA PVT1 in neuropathic pain, which is caused by damage or dysfunction of the nervous system. The researchers found that PVT1 expression was increased with neuropathic pain and that blocking PVT1 reduced pain-related behaviors in these rats (Xu et al., 2021). They also observed that PVT1 may regulate the expression of genes involved in the development and maintenance of neuropathic pain. Another study explored the

role of LncRNA PVT1 in inflammatory pain, which is caused by tissue damage or inflammation (Zhang et al., 2021).

The researchers found that PVT1 expression was increased with inflammatory pain and that inhibiting PVT1 reduced pain-related behaviors and inflammation in these animals (Huang et al., 2020). LncRNA PVT1 may play a role in the development and maintenance of different types of pain, including neuropathic and inflammatory pain, by regulating the expression of genes involved in pain signaling and inflammation. However, more research is needed to fully understand the mechanisms underlying this regulation and to explore the potential therapeutic applications of targeting LncRNA PVT1 in pain management.

2. Methods

2.1 Animals

All rats were classified two parts, including the rats used for CVP model and Dex treatment. The rats were selected from 10±2-week-old healthy male Sprague–Dawley (SD) rats weighing 300±20g. These rats were housed in our laboratory under pathogen-free conditions and had free access to food and water. The rats were housed at 22-24°C and managed on a 12-hour light and dark cycle. The animal protocol for this study was approved by the Institutional Laboratory Animal Ethics Review Committee. Animals were treated in accordance with the relevant provisions of the Guide for the Care and Use of Laboratory Animals (8th edition, National Academy Press).

The various groups of rats included blank group(n=8), CVP group (n=8), CVP +shNC group (n=10), CVP +shPVT1 group (n = 8). The other SD rats were randomly and evenly divided into W1 group was a blank control, W2 group did not establish a CVP model and was injected with 5% 0.3mL DMSO, W3 group was established as CVP model only, W4-CVP group was injected with 5% dimethyl sulfoxide 0.3 mL containing 6μg Dex, W5-CVP group was injected with 5% dimethyl sulfoxide 0.3 mL containing 26μg Dex and W6-CVP group was injected with 52μg of dexmedetomidine in 5% dimethyl sulfoxide 0.3mL.

2.2 Electronic von Frey (VF) test

The mechanical withdrawal threshold (MWT) method was employed to measure mechanical sensitivity in rats. Approximately 15 minutes after acclimation to the experimental environment, the center of the hind paw of each rat was stimulated with Von Frey test probes. The force applied was gradually increased until the rats exhibited a foot withdrawal response. A positive response was defined as the rapid retraction of the foot or biting of the stimulated paw by the rat during the stimulation period or immediately after the

withdrawal of the Von Frey filament. It is worth noting that physical activity-induced foot withdrawal responses were not considered positive responses. The stimulation was repeated five times, with a 30-second interval between each measurement. The threshold for 50% positive response was determined through titration, which refers to the probe stimulation pressure (G) corresponding to the MWT of the rat.

2.3 AWR scores of pain threshold

The abdominal withdrawal reflex (AWR) method was employed to evaluate colonic dilation stimulation in rats. Specifically, a 3 mm diameter and 20 mm long angioplasty balloon was inserted into the anus of each rat and secured to the tail with tape. The AWR scale was used to assess behavioral changes resulting from colonic dilation stimulation. A score of 0 indicated no apparent behavioral change, while a score of 1 indicated simple head movements. Onset of contraction of the abdominal muscles was assigned a score of 2, while a score of 3 indicated significant detachment of the lower abdominal wall from the bottom of the box or a significant flattening of the contraction.

A minimum pressure, corresponding to the pain response threshold, was assigned a score of 4 when the abdominal wall was bowed or when the body and pelvis were flexed. The colonic distension stimuli were set to 80, 60, 40 and 20 mmHg and lasted for 20 seconds with a 5-minute interval between each stimulus. A score of 3 on the AWR scale was recorded when the lower abdominal wall was significantly detached from the bottom of the box or the contraction was significantly flattened.

2.4 Intrathecal Injection

The intrathecal injection was performed using the 5th to 6th lumbar interval as the puncture point, and the needle was inserted vertically by positioning the midpoint of the anterior line of the sacral bones bilaterally as the marker point until the rat's tail showed lateral fluttering or trembling. Next, after securing the catheter and suturing the incision, we proceeded with the gene delivery phase. In order to introduce the LV-shNC and LV-sh-PVT1 lentiviral vectors (1×10^7/0.1 mL) for the purpose of gene delivery, we used a micro-syringe that was connected to an intrathecal catheter. This was done three days before the modeling phase.

2.5 Visceral motor response and mean arterial pressure measurement

Anesthetized rats were connected to a bio-functional experimental system to assess colonic dilation stimulation-induced electromyographic

signals. Mean arterial pressure (MAP) was measured using a tail-sleeve non-invasive blood pressure tester after ether anesthesia. To establish the blood pressure of rats, an electric current was used to heat their tails until the skin had a slight reddish hue. Then, a pressure pulse from a sphygmomanometer was applied at the base of the tail, while a highly sensitive pulse transducer was positioned in the middle third of the tail's ventral side. The systolic and diastolic blood pressures of the rats were observed by intermittently inflating and deflating a balloon, and MAP was determined by analyzing the recordings.

2.6 Quantitative RT-PCR

To isolate total RNA from different groups of rats' spinal cords, around 100 mg of tissue was collected and mixed with 1 ml of TRIzol reagent. The chloroform-75% ethanol method was used to isolate the total RNA from the materials. For miRNA detection, mirPremier® Isolation Kit was used to isolate total RNA. The first-strand cDNASynthesis Kit was used to transcribe the total RNA. qRT-PCR was then performed to analyze the content of PVT1, CXCR5, and GAPDH.

Table 1: Primer sequences

GENE	PRIMER SEQUENCE
PVT1	Forward: 5′- TGAGAACTGTCCTTACGTGACC-3′
	Reverse: 5′-AGAGCACCAAGACTGGCTCT-3′
CXCR5	Forward: 5′-ATCGTCCATGCTGTTCACGCCT-3′
	Reverse: 5′- CAACCTTGGCAAAGAGGAGTTCC-3′
GAPDH	Forward: 5′-GGAGTCCACTGGTGTCTTCA-3′
	Reverse: 5′-GGGAACTGAGCAATTGGTGG-3

2.7 ELISA tests

Initially, 50 to 100 mg of spinal tissue was homogenized in 500 µl of PBS solution using an ultrasonic cell shredder. After centrifugation at 12,000 r/min for 10 minutes at room temperature, the supernatant was collected. To determine the concentration of IL-6, TNF-α, and CXCL13, ELISA was performed according to the instructions of an ELISA kit obtained from Invitrogen, USA.

2.8 Statistical Analysis

Data analysis and graphical representation were conducted using GraphPad 9.4 software, with the application of two-tailed Student's t-test and one-way ANOVA. The measurement data were expressed as mean±standard deviation ($\bar{x}$±s), with statistics considered significant when $P<0.05$.

3. Results

3.1 Expression of PVT1 is increased in CVP rats

In order to investigate the role of PVT1 and CXCR5 in CVP, the rat model with CVP was created. The PVT1 and CXCR5 mRNA was assessed in the rats with CVP, at intervals of 0, 1, 2, and 3 weeks after surgery via qRT-PCR assay. The results showed the significant increase in PVT1 and CXCR5 expressions in the spinal cord of the rats in the CVP group, as compared to the control group (Fig. 1, $P < 0.05$).

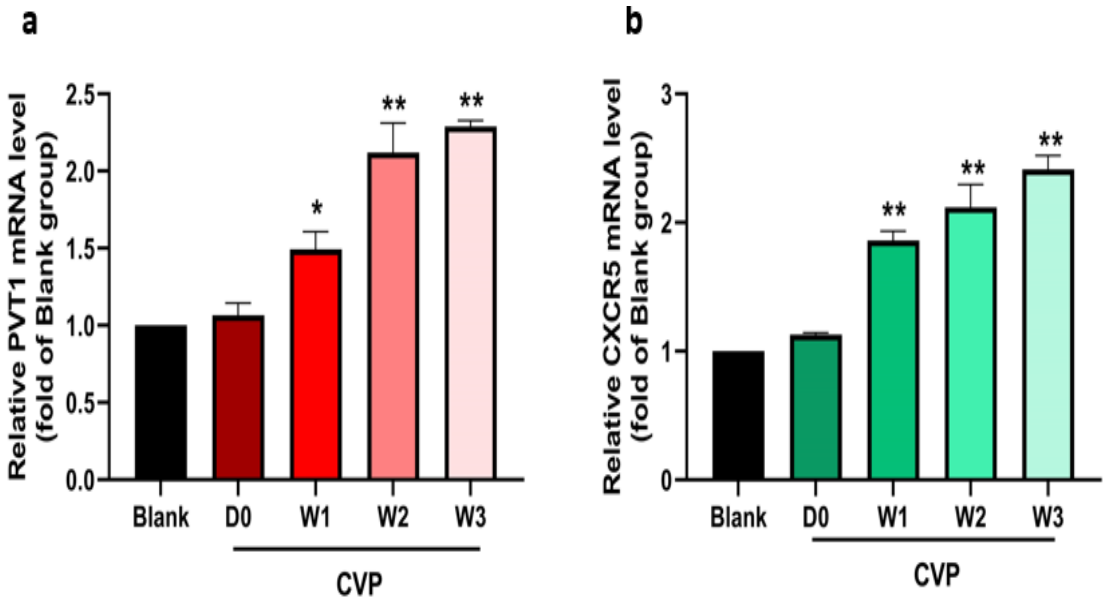

Figure 1: Increased expression of PVT1 and CXCR5 in the spinal cord of rats with chronic visceral pain (CVP) compared to control group.

3.2 Inhibition of PVT1 cause reduction of chronic visceral pain in rat model

To investigate the role of PVT1 in CVP model rats, LV-sh-PVT1 or LV-shNC was administered to CVP rats within the sheath. The expression of PVT1 levels displayed a significant decrease in PVT1 expression was observed in the CVP+LV-shPVT1 group compared to CVP+LV-shNC group (Figure 2a). CXCR5 mRNA levels were assessed using qPCR, revealing that the administration of LV-shPVT1 led to a reduction in CXCR5 mRNA expression (Figure 2b). The pain experienced by the rats was evaluated by monitoring their AWR scores. The AWR scores of rats in the CVP+LV-sh-PVT1 group were significantly lower than those of the CVP+LV-shNC group (Figure 2c). Finally, 50% MWT was employed to assess CVP in each group of rats. After the injection of LV-shPVT1, the MWT of CVP+LV-NC rats enhanced than that CVP+LV-NC rats, indicating alleviation of hyperalgesia (Figure 2d), suggesting that inhibiting PVT1 in rat models reduced the incidence of CVP.

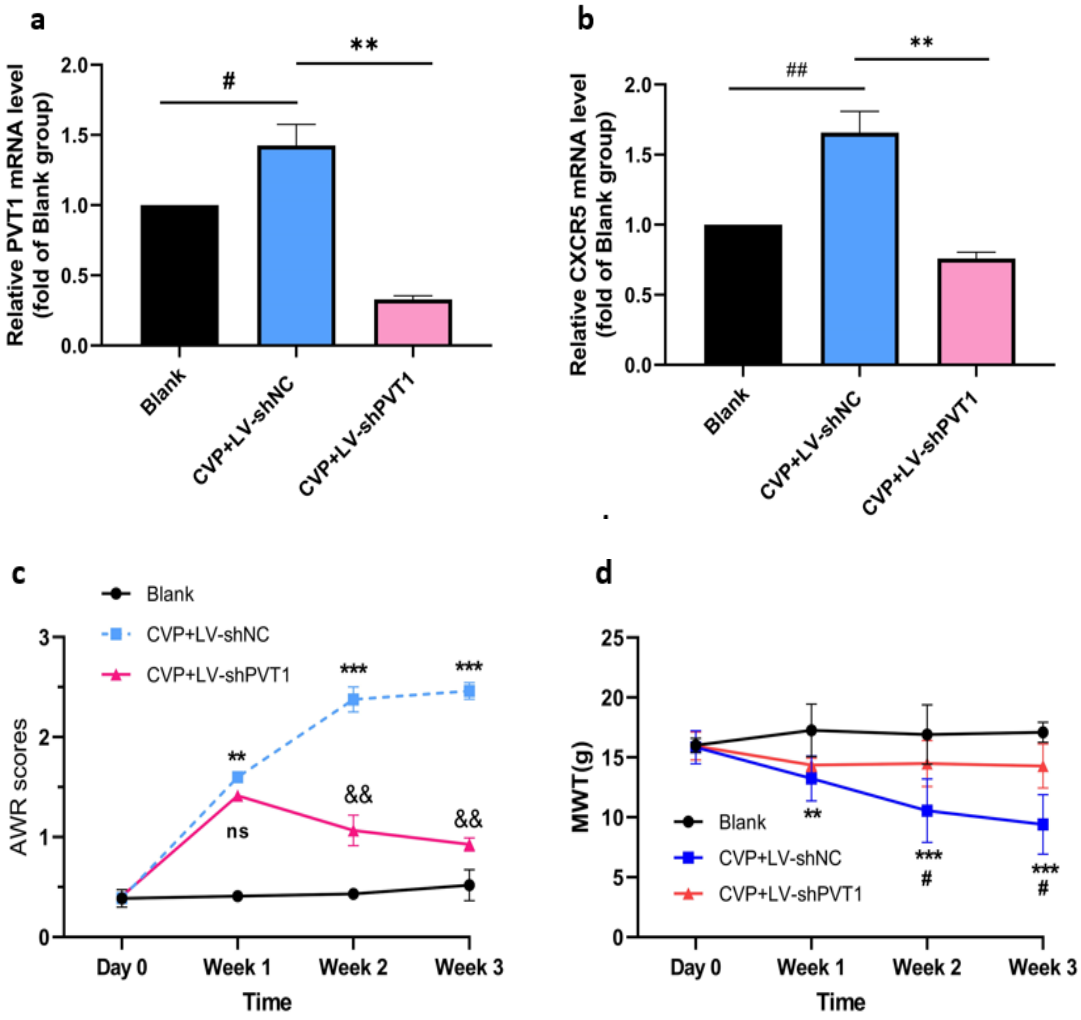

Figure 2: Lentivirus-mediated knockdown of PVT1 alleviates CVP in rats.

*(a) The expression levels of PVT1; (b) CXCR5 mRNA levels; (c) The AWR scores of rats; (&&P<0.01, CVP+LV-shNC vs. CVP+LV-shPVT1). (d) the MWT of rats (#P<0.05, CVP+LV-shNC vs. CVP+LV-shPVT1). **P<0.01 and ***P<0.001, compared with Blank group.*

3.3 Dexmedetomidine treatment can relief CVP and in rat model

The W5 and W6 cohorts had considerably inferior AWR magnitudes juxtaposed to the W3 cohort, while the elevations of TWL and MWT were amplified ($p<0.05$). There were no momentous discrepancies in AWR, TWL, and MTL between the W4 and W3 clusters. The W6 cluster displayed a marked decrease in AWR magnitudes, but an upsurge in TWL and MWT magnitudes collated with the W4 and W5 clusters ($P<0.05$, Figure 3A). The EMG signal magnitudes were significantly curtailed in the W5 and W6 clusters collated with the W3 cohort, and this disparity was statistically weighty ($p<0.05$, Figure 3B). Nevertheless, there were no substantial divergences in EMG signal magnitudes between the W4 and W3 clusters. The W6 cohort displayed significantly inferior EMG signal magnitudes than the W4 and W5 clusters. The distinction in EMG signal magnitudes between the W4 and W3 clusters was statistically salient. As

illustrated in Figure 3C, the MAP magnitudes in cohorts W2, W3, W4, W5, and W6 did not evince a significant deviation from the W1 cohort at 5 minutes. After AWR stimulation, MAP magnitudes were strikingly lower in rats in W5 and W6 clusters than in the W1 cohort ($p<0.05$), and notably lower in W5 and W6 clusters than in the W4 cohort.

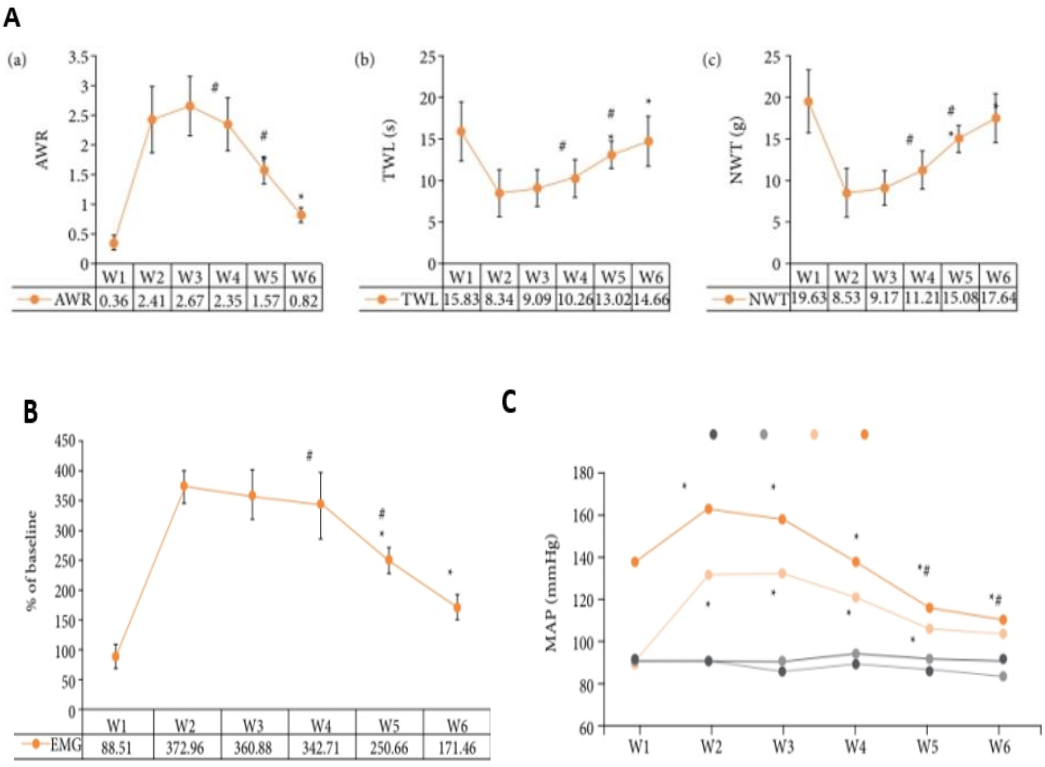

Figure 3: (A) (a) AWR, (b) TWL and (c) MWT in the rat model. * $p<0.05$ when compared to the W3 group. # $p<0.05$ when compared to the W6 group. (B) Electromyographic signal in rats, * $p<0.05$ when compared to the W3 group. # $p<0.05$ when compared to the W6 group. (C) Non-invasive blood pressure in rats (dark grey for 5 min after ether anesthesia, light grey for 5 min after administration of intervention, light orange for 10 min after modeling and dark orange for stimulation of AWR). * $p<0.05$ when compared to W1 group; #$p<0.05$ when compared to W4 group.

3.4 The PVT1 and CXCR5 levels are reduced in the rat model with dexmedetomidine treatment.

To demonstrate the potential molecular mechanisms by which dexmedetomidine alleviates CVP in mice, the levels of PVT1 and CXCR5 were probed in various groups of mice with CVP after treatment. As the results, the highest levels of PVT1 and CXCR5 mRNA were found in the CVP rats without any treatment, indicating that CVP could induce the upregulation of PVT1 and CXCR5 mRNA levels ($p<0.01$). The current data suggest that dexmedetomidine inhibits PVT1 and CXCR5 mRNA levels, with the highest dose being most pronounced in the W6 group (Figure4), suggesting that one of the mechanisms

of dexmedetomidine analgesia may be the inhibition of PVT1 and CXCR5 expression levels.

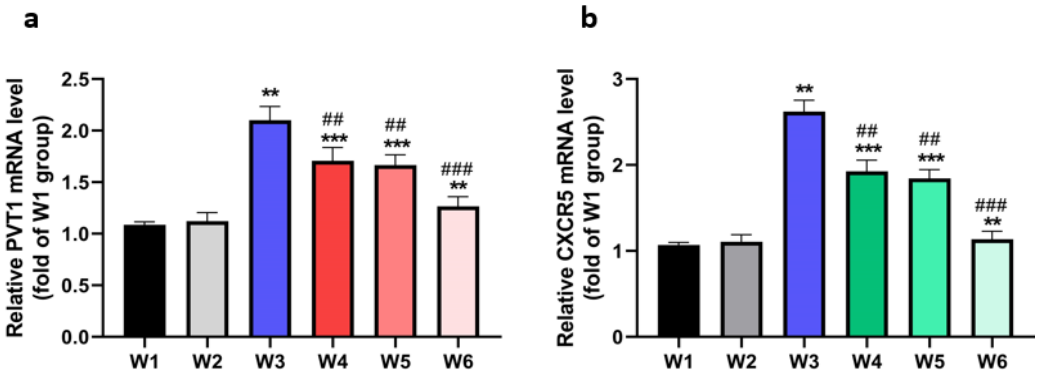

Figure 4: (a) PVT1 and (b) CXCR5 mRNA levels in the in the CVP rat model with dexmedetomidine treatment. ** p<0.01 and ***p<0.001 when compared to W1 group; ## p<0.01 and ###p<0.001 when compared to W3 group.

3.5 Dexmedetomidine treatment reduced the Level of Inflammatory cytokines via PVT1 Inhibition

The levels of IL-6, TNF-α, and CXCL13 in the CVP+Dex group (W6 group) were remarkably decreased compared with the CVP rat group without Dex treatment (W3 group) (Figure 5.). Furthermore, high-dose Dex treatment, which was consistent with W6 group, was used to administered the CVP+LV-shPVT1 rats, levels of IL-6, TNF-α, and CXCL13 could not be inhibited, suggesting that Dexmedetomidine treatment reduced the level of Inflammatory cytokines via PVT1 Inhibition.

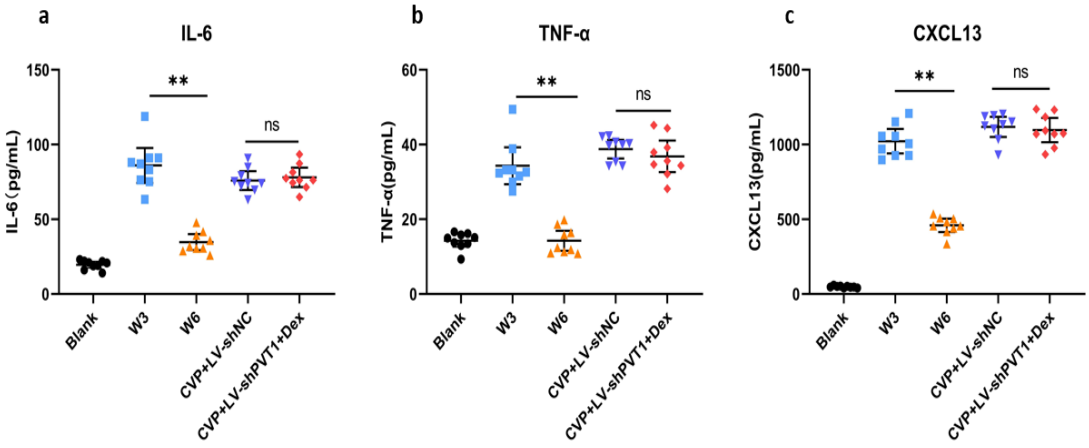

Figure 5: ELISA was conducted to measure the expression levels of inflammatory cytokines including (a) IL-6, (b)TNF-α, and (c)CXCL13.

4. Discussion

The characteristics of CVP are unclear location, often accompanied by pain and physiological/psychological reactions of patients, and relatively

difficult diagnosis and treatment (Kuhlmann et al., 2022). Previous views mostly considered visceral pain as a type of somatic pain, but the mechanisms of these two types of pain. Many diseases in the thoracic, abdominal, and pelvic cavities can cause severe visceral pain in patients. Although with the development of minimally invasive diagnostic and therapeutic technologies such as laparoscopy and endoscopy, the trauma of surgical incisions on patients has been greatly reduced, in laparoscopic and endoscopic surgeries in the thoracic, abdominal, and pelvic cavities, the damage to the viscera and the irritating stimuli have not been significantly improved (Cooper et al., 2017). In addition, due to the inflammation, ischemia, traction, and other reasons of the visceral organs caused by the disease itself and surgery, patients will experience severe visceral pain during the perioperative period. Currently, the opioids are the main drugs used in clinical practice. However, due to the high incidence of adverse reactions of opioids, if used in large quantities for a long time, it will affect the patient's recovery and cause serious complications (Ding et al., 2022). In the 1960s, the first α-2 adrenergic receptor agonist was used to alleviate nasal mucosal congestion. However, drugs such as clonidine, which is a representative of this class, produced some unexpected adverse reactions in clinical use. Nevertheless, since 1966, clonidine has been commonly used for hypotension, and is currently used for drug and alcohol withdrawal. Dexmedetomidine, a highly selective novel alpha-2 adrenergic receptor agonist, which has been widely used in clinical practice, not only has the property of antagonizing sympathetic nerve tension, but also has sedative and analgesic properties (Mahmoud & Mason, 2015; Shehabi et al., 2019). The research findings indicate that α-2 adrenergic receptors are transmembrane receptors composed of G proteins (Bao & Tang, 2020), which act by selectively binding to extracellular ligands and traversing the cell membrane. There are three subtypes of α-2 adrenergic receptors, namely α-2a, α-2b, and α-2c, which can be bound by their respective agonists or inhibitors (Tasbihgou et al., 2021). Pharmacological experiments have revealed that each subtype of α-2 receptor has different physiological functions *in vivo*. Dex mainly acts on α-2a/α2c receptors with a short half-life and strong binding ability. This substance can activate the locus coeruleus in the brainstem by acting on α-2 adrenergic receptors, producing sedative and hypnotic effects. This sedation and hypnosis can be reversed by verbal or external stimuli without respiratory depression. In addition, DEX also has anti-anxiety, stress-reducing, and diuretic effects, but has little impact on the respiratory and circulatory systems (Zhao et al., 2020). According to Tasbihgou et al.'s research, after epidural administration, α-2a adrenergic receptor agonist clonidine can effectively inhibit the release of P substance and glutamate salts from visceral primary afferent fibers, thereby inhibiting central conduction and reducing pain sensitization (Zhang et al., 2015). Moreover, when administered intrathecally, DEX also exhibits dose-dependent inhibition of the external oblique muscle discharge in rats with visceral pain and reduces the abdominal withdrawal reflex score (Scott-Warren

& Sebastian, 2016). Epidural injection of DEX can also inhibit the activation of spinal microglia and astrocytes induced by thermal stimuli, thereby preventing the occurrence of central pain sensitization (Cortínez et al., 2015). According to animal model studies, by applying different doses of epidural α-2a adrenergic receptor agonists, visceral pain sensitization can be prevented, and the central conduction of visceral pain in rats can be inhibited (Li et al., 2021). According to Cortínez et al.'s clinical research, the combination of DEX with local anesthetics (such as ropivacaine, bupivacaine, or lidocaine) can significantly improve intraoperative analgesia, prolong postoperative analgesia time, and reduce the dosage of local anesthetics when administered epidurally, in the sacral canal or intrathecally (Kalpachidou et al., 2020). In addition, DEX has no significant effect on neuromuscular blockade, and has advantages such as circulatory stability, and does not cause significant respiratory depression. In our study, we found Dex can reduce the CVP and inframammary responses in rat models. LncRNAs have been implicated in the development of chronic pain (Yuan et al., 2021). Out of 1327 lncRNAs found to be deregulated in the PBMCs of female patients with diabetic neuropathic pain (DNP), MALAT1, H19, PVT1, and MIR143HG have been identified as potential biomarkers (Chen et al., 2018). PVT1 has been shown to play a role in multiple diseases by modulating inflammatory mechanisms. In the LPS-triggered murine model of septic AKI, PVT1 was discovered to be exceedingly expressed, and curbing of PVT1 was demonstrated to stifle the JNK/NF-κB pathway and diminish LPS-induced inflammatory mediators. In the event of neuropathy associated with diabetes, augmented expression of PVT1 significantly decreased the MWT and TWL and reduced the count of inflammation-related glial cells (Kazanietz et al., 2019). Nevertheless, the function of PVT1 in the context of CVP remains unexplored. Our study revealed that PVT1 was highly expressed in the spinal cord of CVP rats. Inhibition of PVT1 expression via Dex treatment or LV-sh-PVT1 led to a reduction in CVP and decreased the inflammatory response, suggesting that PVT1 may serve as a potent regulator of CVP. CXCL13 was firstly discovered in the stromal cells of B cell follicles, signals through CXCR5, and has a crucial function in the migration of inexperienced B cells and a specific subset of memory T cells to lymphoid tissue. In the SCI model, the depletion of PVT1 considerably alleviated neuropathic pain, astrocytic activation, and decreased the expression of neuro-inflammatory factors and proteins. The pertinent mechanism studies confirmed that PVT1 promotes the expression of CXCL13/CXCR5. This study demonstrates the potential of dexmedetomidine to alleviate chronic visceral pain (CVP) through the modulation of the PVT1/CXCR5 pathway in a preclinical rat model. By increasing pain thresholds, reducing inflammatory markers, and regulating key molecular pathways, dexmedetomidine not only provides significant analgesic effects but also offers a promising approach for enhancing recovery in individuals with chronic pain conditions. These findings underscore the dual benefits of dexmedetomidine in addressing both the physiological and molecular mechanisms underlying CVP.

The implications of this research extend beyond pain management to sports and rehabilitation. Chronic pain often restricts physical activity, delays rehabilitation, and hinders overall performance. By effectively mitigating pain and inflammation, dexmedetomidine has the potential to support individuals, including athletes, in achieving optimal recovery, maintaining physical activity, and enhancing functional outcomes. Future research should explore the clinical applications of dexmedetomidine in sports and physical rehabilitation contexts, particularly its role in facilitating recovery and promoting sustained physical engagement. Additionally, studies on the long-term effects and safety of dexmedetomidine in diverse populations will further solidify its position as a valuable tool in multidisciplinary approaches to pain management and sports medicine.

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