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Therapeutic effects of different doses of peroperative intravenous dexmedetomidine for postoperative incision pain in rats

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Abstract: *It is essential to minimize postoperative pain immediately after an operation. We compared the effects of different doses of preoperative intravenous dexmedetomidine (DMED) on treating postoperative incision pain in rats. Forty healthy, male, and clean-grade Sprague-Dawley rats were randomly divided into five groups: group C, group B, group D1, group D2, and group D3. The rat hind-limb incision pain model was implemented. The cumulative pain score of each group was determined at two h after surgery. Western blotting was used to determine the spinal cord expression of PKC γ, and high-performance liquid chromatography was used to determine spinal cord glutamate levels. Compared with group C, group B had a significantly greater cumulative pain score and greater spinal cord levels of PKCγ and glutamate. There were significantly lower pain scores and levels of PKCγ and glutamate in groups D2 and D3 than in group D1. Perioperative DMED reduced the release of glutamate and inhibited the expression of PKCγ in the rat spinal cord and these changes correlated with reduced postoperative pain. The treatment effect was most evident at the highest tested dose of DMED (1 μg/kg).*

Keywords: *dexmedetomidine, glutamate, protein kinase C, postoperative pain, peroperative, spinal cord, incision pain*

1. Background

Postoperative pain is an acute nociceptive pain that occurs immediately after an operation (1). Previous research reported that 41% of patients have medium-to-severe acute pain after surgery, and 24% of patients do not experience complete relief from pain despite treatment with an analgesic (2, 3). Postoperative pain can lead to anxiety, unease, alterations of the endocrine system, and delayed post-surgical recovery of internal organs. In severe cases, these can increase the risk of serious complications, including myocardial ischemia, accelerated heart rate, pulmonary dysfunction, deep vein thrombosis, and decreased immune function, all of which negatively impact patient prognosis (4, 5). In addition, postoperative pain, if not fully controlled upon onset, may develop into chronic pain and affect the function of multiple organ systems (6). Therefore, effective preoperative analgesia is particularly important.

Clinicians often administer a preoperative intraspinal analgesic because this treatment reduces postoperative pain and is associated with few adverse effects. Intraspinal analgesia is especially suitable for breastfeeding mothers after Cesarean section, elderly patients with cognitive dysfunction, and patients with abnormal liver function (7). Clinicians commonly use local anesthetics and opioids for intraspinal analgesia, but excessive use of these drugs can adversely affect rehabilitation (8-10). Therefore, there is an urgent to identify additional non-opioid analgesics to reduce postoperative pain.

Dexmedetomidine (DMED) is a highly selective adrenalin receptor agonist with sedative, analgesic, anti-anxiety, and anti-sympathetic effects. Previous studies showed that DMED is effective as an anesthetic and postoperative analgesia (11, 12). A recent study showed that DMED effectively relieved chronic pain and reduced glutamate release into the spinal cord (13). An imbalance of intraspinal excitatory amino acids, such as glutamic acid, can lead to central sensitization, a key link in the progression of acute pain to chronic pain (14, 15). Although the intra-spinal application of DMED may

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reduce acute pain, the optimal dosage is unknown.

We compared the effects of different doses of preoperative intravenous DMED on postoperative pain using a rat model of incision pain.

2. Materials and Methods

2.1 Animals

All procedures were according to the protocols of the Guide for the Care and Use of Laboratory Animals (National Research Council, US). Forty adult, male, and clean-grade Sprague-Dawley rats with a normal weight (250–280 g) were housed in pathogen-free conditions at the Animal Center of a University Medical College, in compliance with the Institutional Animal Care and Use Committee (IACUC) regulations (SUMC2017-009). Surgery was performed following anesthesia with 10% chloral hydrate, and efforts were implemented to reduce pain during all procedures. The animals were housed in individual plastic boxes at 24–25°C and given standard chow and free access to water. For drug administration, a catheter was inserted into the L5-6 region and the subarachnoid space of each rat. Rats were randomly assigned to one of 5 groups (8 rats per group): C (no surgery), B (surgery + 1 mL preoperative normal saline), D1 (surgery + 0.5 μg/kg preoperative DMED), D2 (surgery + 0.75 μg/kg preoperative DMED), and D3 (surgery + 1 μg/kg preoperative DMED).

2.2 Intrathecal catheter implantation

For intrathecal anesthesia, a catheter was implanted (16), sevoflurane was administered, and the area was shaved and washed using 75% ethanol. After exposure of the L4-L5 interspinous space and ligamentum flavum, a polyethylene catheter (PE-10; Anlai Company, Ningbo, China) that was connected to a heat source was inserted into the subarachnoid space at L4-L5. A side tail swing or a hind leg twitch determined successful insertion. The catheter was advanced toward the tail by 2 cm, and the outflow of cerebrospinal fluid determined successful insertion. After flushing the catheter with normal saline (10 μL), its distal end was closed and fixed subcutaneously. The catheter tip was at about L3, subcutaneous tunneling. Was used to fix the catheter to the posterior cervical area, and both ends were plugged. Intraperitoneal gentamycin (40,000 IU) was given after the operation. After recovery from the anesthesia, all rats with motor dysfunction were excluded from further experiments.

2.3 Establishment of the incision pain model

The right hind limbs of rats in groups B, D1, D2, and D3 were exposed and disinfected after inhalation anesthesia with sevoflurane. An incision of about 1 cm was made from 0.5 cm to the proximal plantar end to the toe, as described by Brennan et al. (17). After the incision, the plantar muscle was lifted with ophthalmic forceps and cut longitudinally while maintaining the origins, terminations, and attachments of muscles. Compression hemostasis was administered, and the skin was sutured with a fine line. Then, the wounds were disinfected with iodine, and the rats were maintained in a quiet, warm, and sheltered environment. Rats in group C received sevoflurane anesthesia but no surgery.

2.4 Behavioral testing

Rats were kept in a quiet room for 30 min before behavioral testing. A cumulative pain score was used to assess changes in pain behavior beginning two h after surgery. This score (measured for 1 min at 5 min intervals for 60 min) was 0 when there was total loading of the operative hind limb on the surface; 1 when there was merely light touching of the operative hind limb on the surface without twisting; and 2 when the operative hind limb did not touch the surface at all. The most frequent position during each 1 min observation period was recorded. There were 12 observation periods over one h, so the cumulative pain score ranged from 0 to 24 (18). The scoring process was performed by trained staff members blinded to group allocations.

2.5 Western blotting analysis

After the end of the behavioral testing, rats were euthanized, and the caudal L3-L5 segments were rapidly thawed and homogenized in a lysis buffer (4°C). Then, samples were centrifuged for 5 min at 12,000 g (4°C). The protein concentration of the supernatant was measured using the bicinchoninic acid

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(BCA) assay. A total of 30 μg of protein from each sample was loaded into each lane of a 10% SDS-polyacrylamide gradient gel electrophoresis (SDS-PAGE) apparatus (19, 20). The membranes were blocked using 5% skim milk powder (2 h), and then primary rabbit polyclonal antibodies against PKC γ (1:2000 dilution, Abcam) were added before overnight incubation at 4°C. Then horseradish peroxide (HRP) -conjugated goat anti-rabbit (1:5000 dilution, Santa Cruz Biotechnology, USA) IgG (secondary antibody) was added at room temperature (2 h). The enhanced chemiluminescence reagent was added, and the blots were then developed and fixed in a dark room. All target proteins were analyzed by densitometry using Scion Image software (version 4.0.3; Scion Co., USA). The expression of each target protein was calculated relative to GAPDH.

2.6 Sample preparation for high performance liquid chromatography

High-performance liquid chromatography (HPLC) was performed as described by Lu et al. (13). After the end of the behavioral testing and euthanasia, caudal L3-L5 samples were weighed, frozen at -80°C, sonicated in a 0.1 M $HClO_4$ solution with 0.4 mM Na metabisulfite, and then centrifuged for 5 min at 12,000 rpm (room temperature). The supernatant was passed through a Spartan 3/0.2 PA nylon syringe filter (Schleicher & Schuell) and placed on ice until subsequent analysis. Glutamate (Glu), aspartate (Asp), glycine (Gly), and gamma-aminobutyric acid (GABA) were determined simultaneously using an LC-2010CHT Shimadzu system with an ultraviolet detector. Samples (20 μL) were derivatized with ortho-phthalaldehyde (Merck, Darmstadt, Germany) and β-mercaptoethanol (Sigma-Aldrich) in a 0.5 M borate buffer with methanol (1:9) and injected with an autosampler (Merck-Hitachi, LaChrom, L-7250). The separation (mobile phase: binary eluent of 50 mM CH_3COONa [pH 6.5] and methanol) was performed using a VP-ODS column under gradient conditions (CH_3OH, from 26% to 40% over 30 min), during which the column temperature was maintained at 40°C and the flow rate at 1.0 mL/min. All experiments were performed four times, and data were analyzed using the Chromatography Data Station Software (version 3.1.1, Merck-Hitachi Model D-7000).

3. Statistical analysis

Analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). All comparisons of data (presented as means ± standard deviations [SD]) used a one-way analysis of variance and the least significant difference test. A *P* value below 0.05 was considered significant.

4. Results

4.1 DMED relieves postoperative incision pain

We initially compared the cumulative pain scores of rats in the five different groups. The rats in group C (no surgery) normally moved, with both hind limbs fully loaded onto the ground. The rats in group B (surgery + saline) had high pain scores in the hind limb that received surgery and rarely even touched this limb onto the ground. The cumulative pain scores of rats in group D1 (surgery + 0.5 μg/kg DMED), D2 (surgery + 0.75 μg/kg DMED), and D3 (surgery + 1 μg/kg DMED) significantly decreased as DMED dose increased.

4.2 DMED inhibits PKCγ expression in the spinal cord

We next examined the expression of PKCγ in the spinal cords of rats in the five different groups. As with the cumulative pain scores, rats in group B had much greater expression of PKCγ than those in group C. There was also a significant reduction in PKCγ expression as the DMED dose increased.

4.3 DMED reduces glutamate level in the spinal cord

We also examined the glutamate levels in the spinal cords of rats in the five different groups. As with the pain scores and spinal cord levels of PKCγ, rats in group B had much greater spinal cord levels of glutamate than those in group C, and spinal cord glutamate levels significantly decreased as DMED dose increased.

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5. Discussion

Postoperative pain is characterized by a relatively unique peripheral and central molecular mechanism (21), whose pathological basis involves peripheral and central sensitization. Surgical trauma and the consequent inflammation lead to harmful stimulation of the nervous system's external organization and enhanced chemoreceptors' sensitivity in the damaged area, thereby reducing the thresholds for pain in the afferent nerves (22). A peripheral nociceptive stimulus can alter the central nervous system and adversely affect central sensitization, which is characterized by a lower neuronal excitatory threshold, expansion of the area that can provoke excitation, a prolonged neuronal response to painful stimuli, and more prolonged and intense affective experience of pain (23, 24).

PKCγ is a calcium-phosphorus-dependent protein kinase that regulates metabolism, growth, and the proliferation and differentiation of cells by phosphorylation of serine and threonine residues in various regulatory proteins (25). Abundant evidence suggests that PKCγ has roles in the spinal cord's transmission and modulation of nociceptive responses (26-28). In particular, PKCγ can reduce the hyperpathia induced by nerve injury and the allodynia caused by subcutaneous capsaicin injection. Mao et al. (29) used autoradiography to show that spinal cord PKCγ levels were more significant at the site of nerve injury in rats receiving surgery than in rats receiving sham surgery; moreover, gangliosides, which are inhibitors of PKC, reduced this pain. A morphological study confirmed that PKCγ-expressing neurons are present in the ventral part of the spinal cord layer II (30). These results indicate that PKCγ has a significant role in neuronal sensitization and nociceptive pain (31). In agreement with this, another study found that intraspinal application of a PKC inhibitor enhanced the pain-reducing effect of clonidine, and a PKC agonist partially reversed the effect of clonidine (32). These results indicate that proteins in the PKC family play essential roles in resistance to damage of the spinal cord α2 adrenergic receptor (32). Similarly, our results show an increased expression of rat spinal cord PKCγ following induction of acute incision pain and that preoperative intravenous administration of DMED provided an analgesic effect and down-regulated PKCγ. This supports the hypothesis that the analgesic effect of DMED is due to its down-regulation of PKCγ, but further experiments are required for confirmation.

The upregulation of PKC can increase neuronal excitability, inhibit glutamate uptake via the glutamate transporter, and increase the accumulation of extracellular glutamate (33). Glutamate is the primary excitatory neurotransmitter in the central nervous system, and it can bind to the N-methyl-D-aspartic acid (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, leading to the influx of Ca^{2+} (34, 35). Glutamate can also activate phospholipase C via the glutamate receptor in a protein-mediated mechanism, thereby increasing diacylglycerol and nerve cell damage (36). Glutamate release by the sensory afferent nerve endings is the initial factor in pain transmission, and reduced biosynthesis and release of glutamic acid in the neurons by blocking glutamine transport inhibits central nervous system sensitization and produces an analgesic effect (37-39). The present study confirmed that spinal cord glutamate levels were more significant in rats with postoperative incision pain, consistent with previous studies. The present study also found that DMED down-regulated spinal cord glutamate levels and had a potent analgesic effect. Based on our results and the results of previous studies, we speculate that DMED reduces spinal cord glutamate levels by down-regulation of PKCγ.

Based on clinical practice, we selected a dose range of DMED in this study (0.50–1.0 μg/kg). Our results show that animal pain declined as the DMED dose increased. Intra-spinal preoperative administration of 1 μg/kg DMED has apparent therapeutic effects on acute postoperative incision pain in rats. A shortcoming of the present study is that we determined pain for only a brief period (1 h) at two h after surgery, so our results may not apply to all postoperative pain. Furthermore, we did not identify the specific mechanism by which DMED mitigates the upregulation of PKCγ and down-regulates the release of glutamate.

6. Conclusion

In conclusion, our study of a rat model of incision pain demonstrated that intravenous preoperative DMED inhibits the expression of PKCγ, reduces glutamate release into the spinal cord, and reduces acute postoperative incision pain. The analgesic effect of DMED increased to the highest tested dose of 1.0 μg/kg.

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