

Original Article

Anti-nociceptive effects analysis and cognitive impact of dexmedetomidine in rats with neuropathic pain in the sciatic nerve

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Abstract: Objective: The aim of this study was to investigate the anti-nociceptive effects and cognitive impact of dexmedetomidine (Dex) in rats with neuropathic pain in the sciatic nerve. Methods: A total of 120 adult male Wistar rats were randomized into a sham-operated group (SO group, n=40), neuropathic pain model group (NP group, n=40), and Dex injected model group (D group, n=40). A chronic constriction injury (CCI) model was employed for induction of neuropathic pain in NP and D groups. The number of successfully modelled CCI rats in NP and D groups were 38 (95.00%) and 37 (92.50%), respectively. Dex (25 µg/kg) was injected into rats of group D, while rats in the SO and NP groups were injected with an equal volume of normal saline. Mechanical withdrawal threshold (MWT) and thermal withdrawal latency (TWL) of the right hind foot were measured in each rat on the 4th, 7th, 11th, and 14th postoperative days. On the 14th postoperative day, an eight arm radial maze test was performed to measure changes in cognitive function of the rats. The animals were sacrificed immediately after the completion of the eight arm radial maze test and tissues from medial prefrontal cortex encephalic regions were resected. Expression of NR2B mRNA and protein was measured by qRT-PCR and Western blotting, respectively. Results: Compared to the SO group, postoperative threshold of pain in the NP group was significantly reduced ($P<0.05$), cognitive abilities and memory capacities were significantly reduced ($P<0.05$), and expression of NR2B mRNA and protein was significantly increased (both $P<0.05$). On the other hand, postoperative threshold of pain was significantly decreased ($P<0.05$), cognitive abilities and memory capacities were significantly improved ($P<0.05$), and levels of NR2B mRNA and protein were significantly decreased (both $P<0.05$) in the D group compared to the NP group. Conclusion: Dex significantly ameliorates neuropathic pain in the sciatic nerve and cognitive dysfunction in rats with CCI.

Keywords: Dexmedetomidine, neuropathic pain in the sciatic nerve, cognitive function, rat model, mechanical withdrawal threshold, thermal withdrawal latency

Introduction

Neuropathic pain (NP) is a type of chronic and refractory pain that afflicts humans, caused by primary damage or dysfunction of the nervous system. Sciatica is a common type of neuropathic pain [1, 2].

A chronically painful disease with complex pathogenesis, NP can be caused by various diseases and injuries. It is a result of interactions among multiple receptors, neurotransmitters, and signaling pathways. NP can also directly or indirectly injure the nervous system. It is a significant health problem worldwide [3, 4]. Statistics show that incidence rates of NP in devel-

oping countries account for 7% of global incidence, significantly higher than that in developed countries such as the United Kingdom (1%) and United States (1.5%) [5]. Moreover, more than half of the patients in China are unable to relieve pain effectively, seriously affecting their quality of life and increasing economic burden.

Dexmedetomidine (Dex), a new generation of highly selective α_2 -adrenergic receptor agonist, activates α_2 -adrenergic receptors in the peripheral vessels of the central nervous system and inhibits norepinephrine release, thereby producing tranquilizing, analgesic, and antianxiety effects [6]. It also has inhibitory effects on sym-

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Table 1. Primer sequences

| Gene | Upstream primers | Downstream primers |
|----------------|-----------------------------|-----------------------------|
| AQP8 | 5'-TGGTGAGGGGAAGGAGAC-3' | 5'-CACAAATGACAGCCAATAATG-3' |
| AQP9 | 5'-CTCCTGATTATTGTCATTGC-3' | 5'-ATCCACCAGAAGTTGTTT-3' |
| β -actin | 5'-CCTCTGGACACTTGGATATGA-3' | 5'-GGGACGGGGTTGTTGTAG-3' |

Science Instrument Co. Ltd. and Chengdu Taimeng Software Co. Ltd., China, respectively.

Establishment of the rat NP model

pathetic nerve activity and stress response [7]. However, few studies have been conducted on the association of Dex and NP. The underlying mechanisms have not been elucidated. Therefore, this present study established an animal model of NP to explore the effects of Dex on NP, providing an experimental basis for Dex-mediated NP therapy.

Materials and methods

Animals

A total of 120 adult male Wistar rats of SPF grade aged 12-13 weeks, weighing 260 ± 15 g, were adopted for the experiments. All rats were housed in the Animal Experimental Center of Beijing Ditan Hospital, Capital Medical University, in separate cages. The quiet ventilated room was maintained at $23 \pm 3^\circ\text{C}$ with a humidity of 70-80%. Food and water were provided ad libitum. The rats were randomized into 3 groups, sham-operated group (SO group, $n=40$), neuropathic pain in the sciatic nerve model group (NP group, $n=40$), and Dex injected model group (D group, $n=40$). All experiments were conducted according to ethical principles of animal experiments in Beijing Ditan Hospital, Capital Medical University. The study was approved by the Animal Experimental Welfare and Ethics Committee of the hospital.

Main reagents and instruments

Dex was purchased from Jiangsu Hengrui Pharmaceutical Co. Ltd. Reverse transcriptase and reverse transcription kit were purchased from TaKaRa Co. Ltd., Japan. The 2*SYBR Green qPCR Mix and Revert Aid First Strand cDNA Synthesis Kit were bought from Invitrogen Corporation, USA. All primary and secondary antibodies goat anti-NR2B IgG, mouse anti- β -actin IgG, rabbit anti-goat IgG-HRP, and goat anti mouse IgG-HRP were purchased from Beijing Zhongshan Jinqiao Biotechnology Co. Ltd., China. Eight arm radial maze, electronic von Frey aesthesiometer, and PL-200 sting thermal imager were purchased from Shanghai Yuyan

Rats randomized into the NP and D groups were first anesthetized by injections of 2.5% pentobarbital (400 mg/kg). Their right lower limbs were disinfected. The skin of the lower limbs was sheared and muscles were carefully separated (blunt) to avoid massive hemorrhaging. The right sciatic nerve trunk was exposed and freed with a glass needle. A 4-0 thin line was used for ligations at each end of the sciatic nerve stem. The distance between two ligations was 0.1-0.2 cm. Ligation was stopped when the ipsilateral skeletal muscle fibrillation occurred and the incision was sutured and bound up. For rats in the SO group, sciatic nerves were exposed without ligation and the rats were sutured [8].

Administration

Rats in the D group were restrained and tail vein catheters were placed for drug injection. The tails were first disinfected and the bilateral veins at the lower 1/4 (round tail) or 1/2 (bamboo or square tail) part of the tail were exposed. A 24-gauge indwelling needle was used and the inner needle was inserted into the vein at a $20-25^\circ$ angle. When blood flowed out of the indwelling needle, the cannula was inserted and the needle was pulled out. After 3 days of modeling, rats in the D group were injected with Dex (25 $\mu\text{g}/\text{kg}$). Rats in the SO and NP groups were injected an equal volume of saline (tail vein injections).

Measurement of mechanical withdrawal threshold (MWT) and thermal withdrawal latency (TWL)

On the 4th, 7th, 11th, and 14th day after successful modeling, MWT and TWL were measured using the electronic von Frey aesthesiometer and sting thermal imager, respectively. Measurements were performed from 8:00 to 11:00 am the day after Dex injections. Experiments were conducted in a quiet room and all external influences were minimized. For measuring MWT, the rats were placed in a plexiglass cage that was placed on a metal mesh platform for

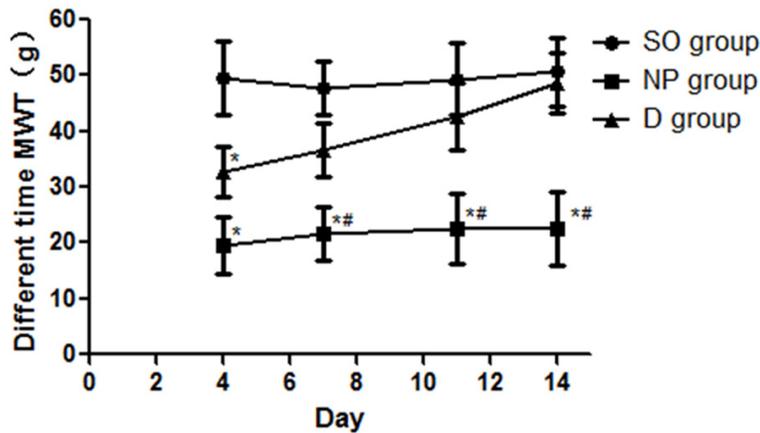


Figure 1. MWT at different times in each group. Compared with SO group, *P<0.05; compared with D group, #P<0.05. MWT, mechanical withdrawal threshold.

10 minutes. The electronic von Frey aesthesiometer was used to stimulate the middle of the right paw surface of each rat in the lower grid and stimulation was gradually increased. Stimulation was stopped when the rat's foot reflex value reached MWT. This experiment was repeated 3 times, lasting for 10 minutes each time. To measure TWL, a foot sting thermal imager was placed at the bottom of the right foot, irradiated with an infrared beam. The time from the start of irradiation until the time the rat lifted its leg was recorded as TWL. The longest duration of infrared irradiation was 15 seconds. The same site was stimulated for 5 minutes each time, at 10-minute intervals [9].

Eight arm radial maze test

The movement of rats in the eight arm radial maze was observed and recorded after NP modelling. For one week prior to modeling, all rats were trained in the eight arm radial maze twice a day, between 8 to 10 am and 3 to 5 pm. The rats were fasted the day before the start of training. They were left in the maze for 15 minutes to find food. Food was kept at arms 1, 3, 5, and 7 on day 2 of training and several rats were in the maze to find food. From day 4 onward, each rat was individually trained with the above methods until the end of training. One day after successful NP modeling, the rats were tested for memory function. Working memory error (WME), reference memory error (RME), and total memory error (TE) were documented via their movements in the maze, recorded by a

camera system. If a rat entered an arm and ate the food placed there, its memory was correct. If a rat entered the arm where the food was already eaten, it was recorded as WME. If a rat entered an arm where no food was ever kept, it was recorded as RME. The sum of RME and WME was calculated as TE [10].

Relative expression of NR2B mRNA in mPFC encephalic region of the rats tested by qRT-PCR

Total RNA extraction: On day 14 post-operation, the rats were anesthetized (2.5% pentobarbital, 400 mg/kg) after the eight arm radial maze test. After decapitation, the medial prefrontal cortex (mPFC) encephalic region tissue was resected and a part of the tissues were stored at -20°C. The remaining was triturated repeatedly using a grinding rod. Total RNA was extracted from tissue fragments using TRIzol Reagent for 30 minutes. Purity and concentration of extracted total RNA were determined by UV spectrophotometry. When OD₂₆₀/OD₂₈₀ ratio was 1.8-2.1, the RNA was regarded as high quality.

Transcription of cDNA: RNA (1 µg per sample) was reverse transcribed into cDNA with the Revert Aid First Strand cDNA Synthesis Kit, according to manufacturer instructions. Reaction conditions were: 60 minutes at 42°C, 5 minutes at 25°C, 60 minutes at 42°C, and 4°C for preservation. cDNA was stored at -80°C for further use.

qRT-PCR: Experiments were according to the kit cDNA synthesis and in strict accordance with kit instructions. AQP8 and AQP9 RT-PCR primers were designed and synthesized by the Shanghai Shenggong Biotechnology Co., Ltd. This 20.0 µl reaction mix consisted of 2.0 µl DNA template, 3.0 µl of each primer, 2.0 µl 2X dNTP, 5.0 µl 10X PCR buffer, 3.0 µl MgCl₂, and 0.5 µl Taq DNA polymerase. It was prepared to a final volume of 35.5 µl with nuclease-free water. RT-PCR conditions were: pre-denaturation for 3 minutes at 94°C, followed by 40 cycles of 95°C for 30 seconds, 60°C for 30

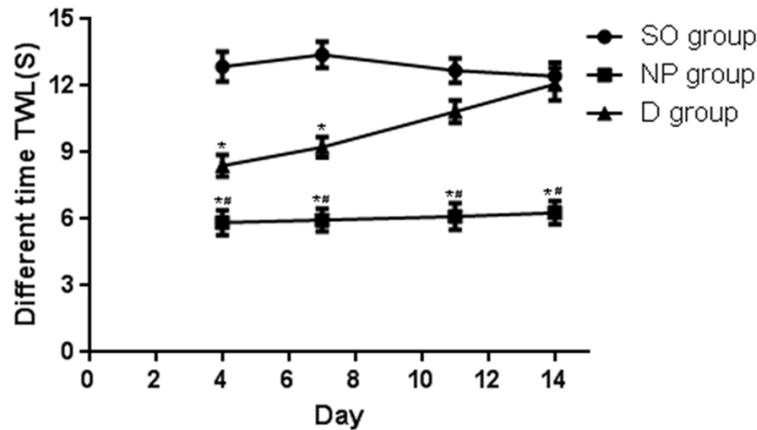


Figure 2. TWL at different times in rats of each group. Compared with SO group, * $P < 0.05$; compared with D group, # $P < 0.05$. TWL, thermal withdrawal latency; SO group, sham-operated group; NP group, neuropathic pain in the sciatic nerve model group; D group, Dex injected model group.

seconds, and 60°C for 45 seconds. GAPDH was used as the internal control. Relative gene expression levels were calculated using $2^{-\Delta\Delta Ct}$. Primer sequences are listed in **Table 1**.

Relative expression of NR2B protein in mPFC encephalic region of the rats tested by Western blot

Frozen brain tissues were thawed, chopped, and homogenized in EP tubes with RIPA buffer and PMSF preservative on ice using a homogenizer. The lysates were then ultra-centrifuged at 11,500 rpm for 5 minutes at 4°C. Supernatants were collected. Protein contents of the clear lysates were quantified using the BCA method and 30.0 μ l of each sample was separated using SDS-PAGE for 90 minutes. Proteins were then transferred to a PVDF membrane for 2 hours. The membrane was blocked for 1 hour with 5% skim milk. The membrane was incubated overnight with primary antibody (1:200) and anti- β -actin antibody (1:2,000) at 4°C. It was then washed three times with TBST, 3 minutes each time. The secondary antibody and HRP conjugated antibody (both 1:2,000) were then added. The membrane was incubated at room temperature. Specific bands were visualized with the ECL chemiluminescent system in a dark room.

Statistical analysis

SPSS 22.0 software package was used to analyze collected data and GraphPad Prism 5 was

used to plot graphs. Measurement data are expressed as mean \pm standard deviation ($\bar{x} \pm sd$). Measurement data of the two groups were compared using t-test and expressed as t when they met normal distribution. All three groups were compared using single factor ANOVA and expressed as F. Intragroup comparisons were conducted by repeated ANOVA measures. $P < 0.05$ is considered statistically significant.

Results

Modeling and results of MWT and TWL

After stimulating the rats of each group, MWT and TWL were measured. Compared to the SO group, MWT and TWL were significantly decreased in NP and D groups (all $P < 0.05$). The decline of MWT on the 4th day post-operation was most significant, showing successful NP modeling. Rats showed the symptoms of toe flexion, limping, and unwillingness to touch the ground. In addition, the rats also showed a conservation-withdrawal reaction. During the study duration, 2, 3, and 1 rats had died, respectively, in the SO, NP, and D groups. Compared to the NP group, expression of MWT and TWL in D group on the 4th day was significantly improved (both $P < 0.05$).

Taken together, from the 7th day to the 14th day after successful modeling, there were no differences in MWT between the D and SO groups. On the 14th day, there were no differences in TWL of D and SO groups (both $P > 0.05$). See **Figures 1 and 2**.

On the 4th day after successful modeling, MWT in the SO group was significantly different from that of the NP and D groups ($F = 25.46$, $P = 0.01$, $t = 3.56$, $P = 0.01$, $t = 2.11$, $P = 0.04$). There was a significant difference between the NP and D groups as well ($t = 1.92$, $P = 0.06$). On the 7th day, MWT of the SO group was different than that of the NP group, but no differences were seen between the SO and D groups ($F = 22.84$, $P = 0.01$, $t = 3.81$, $P = 0.01$, $t = 1.64$, $P = 0.10$). However, MWT was significantly different between

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Table 2. Expression in dark box in group D, group SO, and group NP (time)

| Group | WME | TE | RME |
|-----------------|------------|------------|------------|
| Group SO (n=38) | 0.16±0.05 | 0.11±0.03 | 0.21±0.07 |
| Group NP (n=37) | 0.54±0.07* | 0.35±0.05* | 0.86±0.13* |
| Group D (n=39) | 0.19±0.04# | 0.15±0.03# | 0.25±0.07# |
| F | 14.59 | 12.54 | 14.63 |
| P | 0.01 | 0.01 | 0.01 |

Note: *Represented SO group and NP group compared with D group, $P < 0.01$; #represented NP group compared with D group, $P < 0.01$. WME, working memory error; RME, reference memory error; TE, total memory error.

Table 3. Relative expression of NR2B mRNA in mPFC encephalic region of the rats

| Group | NR2B/GAPDH | F | P |
|-----------------|------------|------|------|
| Group SO (n=38) | 0.58±0.08 | 4.97 | 0.01 |
| Group NP (n=37) | 0.94±0.11 | | |
| Group D (n=39) | 0.65±0.06 | | |

Note: mPFC, medial prefrontal cortex.

Table 4. Relative expression of NR2B protein in mPFC brain region of each group

| Group | NR2B/ β -actin | F | P |
|-----------------|----------------------|------|------|
| Group SO (n=38) | 0.45±0.08 | 3.99 | 0.02 |
| Group NP (n=37) | 0.87±0.15 | | |
| Group D (n=39) | 0.52±0.10 | | |

Note: mPFC, medial prefrontal cortex.

the NP and D groups on day 7 ($t=2.19$, $P=0.03$). Similar trends were seen on the 11th day, ($F=16.30$, $P=0.01$, $t=2.97$, $P=0.01$, $t=0.76$, $P=0.45$), while there were significant differences between NP and D groups ($t=2.36$, $P=0.02$). Finally, on the 14th day, rats in the SO and D group had similar MWT ($F=13.69$, $P=0.01$, $t=3.11$, $P=0.01$, $t=0.24$, $P=0.81$), while there were significant differences between the NP and D groups ($t=3.10$, $P=0.01$).

On the 4th day after successful modeling, TWL in the SO group was significantly different from that of NP and D groups ($F=38.64$, $P=0.01$, $t=7.97$, $P=0.01$, $t=5.39$, $P=0.01$). There was a significant difference between the NP and D groups as well ($t=3.43$, $P=0.01$). This pattern persisted on the 7th and 11th day, with significant differences in TWL between the SO group and NP and D groups (day 7: ($F=29.35$, $P=0.01$, $t=9.27$, $P=0.01$, $t=2.49$, $P=0.01$); day

11: ($F=25.68$, $P=0.01$, $t=8.08$, $P=0.01$, $t=0.76$, $P=0.45$)), as well as between the NP and D groups (day 7: ($t=6.07$, $P=0.01$); day 11: ($t=2.36$, $P=0.02$)). On the 14th day, TWL in the SO group was significantly different than that in the NP group, but there were no significant differences compared with the D group ($F=23.94$, $P=0.01$, $t=7.54$, $P=0.01$, $t=0.38$, $P=0.71$). TWL was significantly different between the NP and D groups ($t=6.42$, $P=0.01$).

Eight arm radial maze experiment conditions

WME in group D was significantly greater than that of SO and NP groups, showing a significant difference ($F=14.59$, $P=0.01$). However, TE in D group was significantly decreased compared to the SO and NP groups ($F=12.54$, $P=0.01$). The number of RME in group D was significantly decreased compared to the SO and NP groups ($F=14.63$, $P=0.01$). Pairwise comparisons of WME in the different groups indicated significant differences between SO and NP groups ($t=4.44$, $P=0.01$), no differences between SO and D groups ($t=0.47$, $P=0.64$), and significant differences between D and NP groups ($t=4.40$, $P=0.01$). Pairwise comparisons of TE in the different groups indicated significant differences between SO and NP groups ($t=4.14$, $P=0.01$), between SO and D groups ($t=0.94$, $P=0.35$), and between D and NP groups ($t=3.47$, $P=0.01$). Pairwise comparisons of RME in the different groups indicated significant differences between SO and NP groups ($t=4.43$, $P=0.01$), no differences between SO and D groups ($t=0.61$, $P=0.55$), and significant differences between D and NP groups ($t=4.05$, $P=0.01$) as shown in **Table 2**.

Relative expression of NR2B mRNA in mPFC encephalic region of rats tested by qRT-PCR

qRT-PCR showed significant differences in levels of NR2B mRNA between the three groups ($F=0.97$, $P=0.01$). Relative expression of NR2B mRNA (NR2B/GAPDH) in the mPFC encephalic region of SO rats was significantly lower than that in the NP group ($t=2.66$, $P=0.01$). No differences were seen in relative expression of NR2B mRNA between the SO and D groups ($t=0.70$, $P=0.48$). NR2B mRNA levels were significantly higher in the NP group than the D group ($t=2.37$, $P=0.02$) as shown in **Table 3**.

Relative expression of NR2B protein in mPFC encephalic region of rats tested by Western blot

Levels of NR2B protein in the mPFC encephalic region were significantly different among the three groups ($F=3.99$, $P=0.02$). Pairwise comparisons between groups showed significantly higher NR2B levels (NR2B/ β -actin) in the SO group compared with the NP group ($t=2.49$, $P=0.02$) and the D group ($t=2.02$, $P=0.05$). No differences were seen in NR2B protein levels between the SO and D groups ($t=0.47$, $P=0.64$) as shown in **Table 4**.

Discussion

Epidemiological studies have shown that more than 16 million people suffer from NP in China, one of the countries with a very high number of NP patients [11, 12]. Clinical manifestations of NP are diverse. The most common symptoms are sciatica, trigeminal neuralgia, and cancerous pain [13, 14]. This present study investigated possible ameliorative effects of Dex on NP in a CCI animal model, similar to the human NP condition. It was a simple, effective, and reproducible model. CCI rats gradually developed pain responses from 5 to 7 days after model establishment, peaking between 10 to 14 days without autophagy [15]. In addition, it showed significantly lower MWT and TWL, indicating successful establishment of the NP model, in accordance with the needs of this experiment.

Dex, a recently identified highly selective $\alpha 2$ adrenergic receptor agonist, is an ideal sedative and analgesic medication by intravenous administration. It has been widely used in intensive care units and postoperative analgesia adjuvant therapy [16, 17]. Studies have shown that Dex not only has tranquilizing and analgesic effects but also inhibits sympathetic nerve activity with anti-anxiety effects [18]. The latter is clinically significant because inhibiting sympathetic nerve activity during surgery can improve the stability of the cardiovascular system. In this study, the threshold of pain in D group was significantly lower than in the NP group, while no differences were seen between the D and SO groups. This clearly indicates the inhibitory effects of Dex on NP. This study also examined the cognitive function of rats with the eight arm radial maze test. It was found that

the cognitive ability of rats in the NP group was decreased significantly on the 14th day after surgery, compared with SO and D groups. No differences were seen in cognitive function between the D and SO groups, indicating that cognitive function of NP in modelled rats improved after Dex injections.

NMDA receptor, a specific excitatory amino acid receptors, is composed of NR1, NR2 (A-D), and NR3 (A-B) in the NRs family [19]. Helion et al. found that NR2B plays an important role in the occurrence and conductive process of NP [20]. In addition, recent studies have shown that mPFC participates in the process of decision-making and emotion regulation [19, 20]. However, the relationship between expression of NR2B in mPFC encephalic region and cognitive function of NP remains unclear. This study analyzed expression of NR2B mRNA and proteins in the mPFC encephalic region of rats, finding that relative expression of NR2B mRNA and proteins in the NP group was significantly increased. This correlated with cognitive dysfunction and hyperalgesia in the rats. However, relative expression levels of NR2B in the SO and D groups were significantly decreased, further proving the association between expression of NR2B in the mPFC encephalic region and cognitive function and hyperalgesia. It can be speculated that NR2B in mPFC encephalic region may also be involved in the formation of NP.

However, this present study has certain limitations. The study was conducted on animals. There was concern whether the results could be extrapolated to clinical studies. NP is a chronic disease but the duration of NP in the CCI model only lasted 2 months. Therefore, the next study should fill the above gaps, through clinical trials, and conduct in-depth mechanistic analysis on the relationship between NP and NR2B. A more effective method should be chosen to construct models to support these research results.

In conclusion, Dex has significant ameliorative effects on rats with neuropathic pain in the sciatic nerve, improving their cognitive function.

Disclosure of conflict of interest

None.

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