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Upregulation of tumor necrosis factor-alpha in nucleus accumbens attenuates morphine-induced rewarding in a neuropathic pain model

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ABSTRACT

Treatment of neuropathic pain with opioid analgesics remains controversial and a major concern is the risk of addiction. Here, we investigated this issue with spared nerve injury (SNI) model of neuropathic pain in rats and mice. SNI prevented conditioned place preference (CPP) induced by low dose (3.5 mg/kg) of morphine (MOR), which was effective for anti-allodynia, but not by high dose ($\geqslant$5.0 mg/kg) of MOR. Tumor necrosis factor-alpha (TNF-α) was upregulated in nucleus accumbens (NAcc) following SNI. The inhibitory effect of SNI on MOR-induced CPP was blocked by either genetic deletion of TNF receptor 1 (TNFR1) or microinjection of anti-TNF-α into the NAcc and was mimicked by intra-NAcc injection of TNF-α in sham rats. Furthermore, SNI reduced dopamine (DA) level and upregulated dopamine transporter (DAT) in the NAcc, but did not affect total tyrosine hydroxylase (TH) or phospho-TH (*p*-TH), a rate-limiting enzyme of catecholamine biosynthesis, in ventral tegmental area (VTA). Accordingly, the increase in DA reuptake but not decrease in its synthesis may lead to the reduction of DA level. Finally, the upregulation of DAT in the NAcc of SNI animals was again blocked by either genetic deletion of TNFR1 or NAcc injection of anti-TNF-α, and was mimicked by NAcc injection of TNF-α in sham animals. Thus, our data provided novel evidence that upregulation of TNF-α in NAcc may attenuate MOR-induced rewarding by upregulation of DAT in NAcc under neuropathic pain condition.

1. Introduction

The treatment of neuropathic pain resulted from peripheral nerve injury remains a big challenge in clinic. Opioid analgesics are the most effective agents for dealing with moderate to severe pain, but the major problem of these substances is the risk of addiction [1]. Many clinical and experimental studies have addressed this issue and suggested that the addictive behavior is attenuated in neuropathic pain condition [2,3]. However, the underlying mechanisms remain elusive.

Dopaminergic projection from VTA to NAcc, a major substrate for rewarding, is critical for drug addiction. In general, the drugs stimulate DA release in NAcc in humans, nonhuman primates and rodents [4–6]. A previous work has shown that the attenuation of MOR-induced rewarding under neuropathic pain may be resulted from reduced DA level in NAcc [3]. The change in DAT, which reuptakes DA to presynaptic terminals, is considered to play a key role in regulating drug rewarding [7,8].

In recent years, accumulating evidence has shown that the over-expression of proinflammatory cytokines, such as TNF-α, is not only necessary but also sufficient for development of neuropathic pain [9] and memory deficits [10] produced by peripheral nerve injury. Nakajima et al. have shown that TNF-α prevents methamphetamine (METH)-induced drug dependence and neurotoxicity through inhibiting the METH-induced increase in extracellular DA levels by the activation of DAT as well as vesicular monoamine transporter-2 [11]. As it has been shown that TNF-α is increased systemically in both patients and animals with neuropathic pain [12,13], in the present work, we tested the hypothesis that the over-expression of TNF-α in mesolimbic DA system caused by nerve injury might attenuate the MOR-induced rewarding.

2. Materials and methods

2.1. Animals

Experiments were performed on adult male Sprague–Dawley rats (200–300 g) and adult male BALB/c mice (20–25 g), obtained

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from Institute of Experimental Animal of Sun Yat-Sen University. Adult male TNFR1-knockout (KO) mice (20–25 g) were obtained from the Jackson's laboratory. The animals were housed in separated cages with access to food and water *ad libitum*. The room was kept at 23 ± 1 °C and 50–60% humidity, under a 12-h light/dark cycle (06:00–18:00 h). All experimental procedures were approved by the Local Animal Care Committee.

2.2. Spared nerve injury

Spared nerve injury (SNI) was carried out following the procedures described by Decosterd and Woolf [14]. Under anesthesia with chloral hydrate (0.4 g/kg, i.p.), the skin on the lateral surface of the left thigh was incised and a section was made directly through the biceps femoris muscle to expose the sciatic nerve and its three terminal branches: the sural, common peroneal and tibial nerves. The common peroneal and the tibial nerves were tight-ligated and sectioned distal to the ligation, removing a 2 mm length of each nerve. During the operation, any contact with or stretching of the intact sural nerve should be avoided. Then the wound was closed in two layers. In sham-operated animals, the nerve was exposed only.

2.3. Measurement of mechanical allodynia

Mechanical pain thresholds in ipsilateral hindpaws were assessed with the up-down method described previously [15] by using Von Frey hairs. Briefly, animals were placed in separate transparent chambers positioned on a wire mesh floor and habituated for 5 min. Each stimulus consisted of a 6–8 s application of the Von Frey hair to the sciatic innervation area of the hindpaws with a 5 min interval between stimuli. The middle stimulus of the series was applied first. In the event of paw withdrawal absence, the next stronger stimulus was chosen. Quick withdrawal or licking of the paw in response to the stimulus was considered a positive response.

2.4. Conditioned place preference (CPP)

CPP test was performed in the apparatus equipped with an automatically monitoring system (Jiliang, Shanghai, China). The apparatus consisted of two compartments of the same size ($30 \times 30 \times 53$ cm^3 for rats and $10 \times 10 \times 15$ cm^3 for mice) with a door in the central partition (1 cm thick). One side was white with a textured floor and the other side was black with a smooth floor. The CPP test is consisted of the following phases (see Fig. 1). In preconditioning phase (postoperative day 5–7), the animals were habituated to the apparatus for 50 min daily for 2 days and on postoperative day 7 animals were placed in the white compartment and were allowed to move freely in the apparatus for 15 min. Record the time spent in white compartment of each animal as the preference score. In the conditioning phase (postoperative day 8–12), animals were injected saline in the morning and immediately confined to the black compartment for 30 min, and in the afternoon (about 6 h later), the same animals were injected morphine (3.5 mg/kg, 5.0 mg/kg or 7.5 mg/kg, s.c.) and were immediately confined in the white compartment for 30 min on postoperative day 8. On postoperative day 9, the same experiments were carried out, but the animals received morphine in the morning and saline in the afternoon. Above experimental procedure was repeated in remaining days. Control animals received only saline but no morphine. In postconditioning phase (postoperative day 13), preference score of each animal was measured.

2.5. Micro-infusion procedures

Animals were anaesthetized with chloral hydrate (0.4 g/kg, i.p.) and stereotaxic surgeries were performed according to the brain atlas. Permanent guide cannulas were implanted bilaterally 1 mm above NAcc or VTA and secured with dental acrylic cement. The stereotaxic coordinate for NAcc and VTA were as follows: AP + 1.6 mm, ML ± 2.0 mm, DV − 6.7 mm; AP − 5.6 mm, ML ± 1.0 mm, DV − 8.0 mm. After surgery, the rats were housed individually and allowed to recover for 7 days. Animals were administered rrTNF-α (1 μg/ml, 1 μl, R&D) or artificial cerebrospinal fluid (aCSF; NaCl 124 mM, KCl 3.3 mM, KH_2PO_4 1.2 mM, $NaHCO_3$ 26 mM, $CaCl_2$ 2.5 mM, $MgSO_4$ 2.4 mM) (1 μl) twice a day 5 min before morphine or saline during the conditioning phase (Fig. 1A). Anti-TNF-α (250 μg/ml, 1 μl, R&D) or IgG (250 μg/ml, 1 μl, R&D) were injected into NAcc in 60 s 2 h before SNI and daily for the next 12 days (Fig. 1B).

2.6. TNF-α bioassay

After animals were anesthetized with urethane (1.5 g/kg, i.p.), brains were removed from decapitated animals on the postoperative day 7 and sectioned in a cryostat to the rostral end of the NAcc (shell; 1.2–1.7 mm relative to the bregma) and VTA (−5.20 to −6.04 mm relative to the bregma). Tissue punches were homogenized in ice-cold PBS followed by centrifugation at 4 °C for 15 min (12,000 rpm). The supernatant was used to measure the concentrations of TNF-α by using anti-rat TNF-α ELISA Kits (R&D) according to the manufacturer's protocol.

2.7. Western blot

The brains were removed from decapitated animals and sliced to obtain NAcc and VTA. Samples were homogenized in 15 mM Tris buffer, pH 7.6 [250 mM sucrose, 1 mM $MgCl_2$, 1 mM DTT, 2.5 mM EDTA, 1 mM EGTA, 50 mM NaF, 10 μg/ml leupeptin, 1.25 μg/ml pepstatin, 2.5 μg/ml Aprotin, 2 mM sodium pyrophosphate, 0.1 mM $NaVO_4$, 0.5 mM PMSF, and protease inhibitor cocktail (Roche Molecular Biochemicals)]. The tissues were sonicated and centrifuged at 12,000 rpm for 15 min at 4 °C to isolate the supernatant containing protein samples. Proteins were separated by gel electrophoresis (SDS–PAGE) and transferred onto a PVDF membrane (Bio-Rad). The membrane was immunoblotted with DAT antibody (1:200, Millipore), *p*-TH Ser40 antibody (1:1000, R&D), TH antibody (1:200, Santa Cruz) and β-actin antibody (1:1000, Cell Signaling Technology). Protein bands were detected by ECL (Pierce, USA) and exposed to X-ray film (Kodak). Integrated optical densities were analyzed by Image-Pro Plus software 6.0 (Media Cybernetics).

2.8. Dopamine microdialysis

Animals were anaesthetized with chloral hydrate (0.4 g/kg, i.p.) and the intracerebral guide cannulas (MD - 2251; BASi) were implanted bilaterally 1 mm above NAcc (AP + 1.6 mm, ML ± 2.0 mm, DV − 6.7 mm) and secured with dental cement. Three days after the operation, microdialysis was done in wake, freely moving animals. The microdialysis probe (MD − 2200; BASi) with 2 mm of semipermeable membrane projecting beyond the guide cannula was inserted and perfused continuously with aCSF at the speed of 1 μl/min. After a 90-min wash out period, dialysate was collected in 30-min fractions. For the measurement of DA levels, 7.5 μl sample was injected into the high-performance liquid chromatography with electrochemical detection (HPLC-ECD) system (BASi) with a mobile phase (3.28 mM sodium heptanesulfonate, 0.16 mM EDTA, 100.81 mM sodium acetate, 93 mM citric acid and 8% methanol, pH 3.7). Six samples were used to establish baseline levels of extracellular DA 1 day before SNI or sham operation. Dopamine concentrations were expressed as percent of the corresponding baseline level.

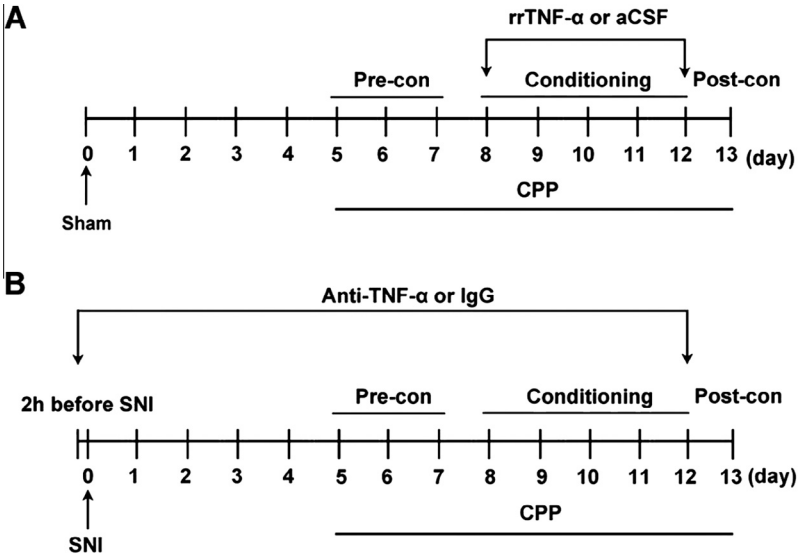

Fig. 1. Experimental schedules. (A) The schedules for the study of the effects of rrTNF-α on MOR-induced CPP in sham rats. (B) The schedules for the study of the effects of anti-TNF-α on MOR-induced CPP in SNI rats.

2.9. Statistical analysis

The data are presented as the means ± SEM. The statistical significance of differences between the groups was assessed by two-way analysis of variance (ANOVA) followed by the Bonferroni/Dunnett's test or Student's *t*-test. $p < 0.05$ was considered statistically significant.

3. Results

3.1. The effects of SNI on the rewarding induced by different dosages of morphine in rats

To test whether the effect of neuropathic pain on the MOR-induced rewarding is dependent on the dosage of morphine, CPPs induced by different doses of MOR were measured in sham and SNI rats 7 days after the operation. As shown in Fig. 2A, compared with saline controls, the preference scores in 3.5 mg/kg group were significantly higher in sham rats ($p < 0.05$) but not in SNI rats ($p > 0.05$), and the scores in SNI rats were not different from those of saline controls ($p > 0.05$), indicating that CPP induced by this dose of MOR was prevented by SNI. Whereas, the preference scores in both sham and SNI rats of 5 mg/kg and 7.5 mg/kg MOR groups were significantly higher than those of saline control groups ($p < 0.05$ and $p < 0.01$, respectively), and there was no difference between SNI and sham rats ($p > 0.05$). The data suggested that SNI failed to prevent the CPP induced by the high doses of MOR. To evaluate the analgesic effects of the three doses of MOR on sham and SNI rats, the mechanical paw withdrawal thresholds were tested 30 min and 70 min after MOR application. As shown in Fig. 2B, at 30 min after application, the paw withdrawal thresholds at each of three doses of MOR were significantly higher in SNI rats, compared to saline control rats ($p < 0.01$) and were not different from those in sham rats ($p > 0.05$), suggesting that the mechanical allodynia is completely reversed. Seventy minutes after MOR, however, the paw withdrawal thresholds of SNI rats in 5 mg/kg and 7.5 mg/kg groups still remained the same level, while the

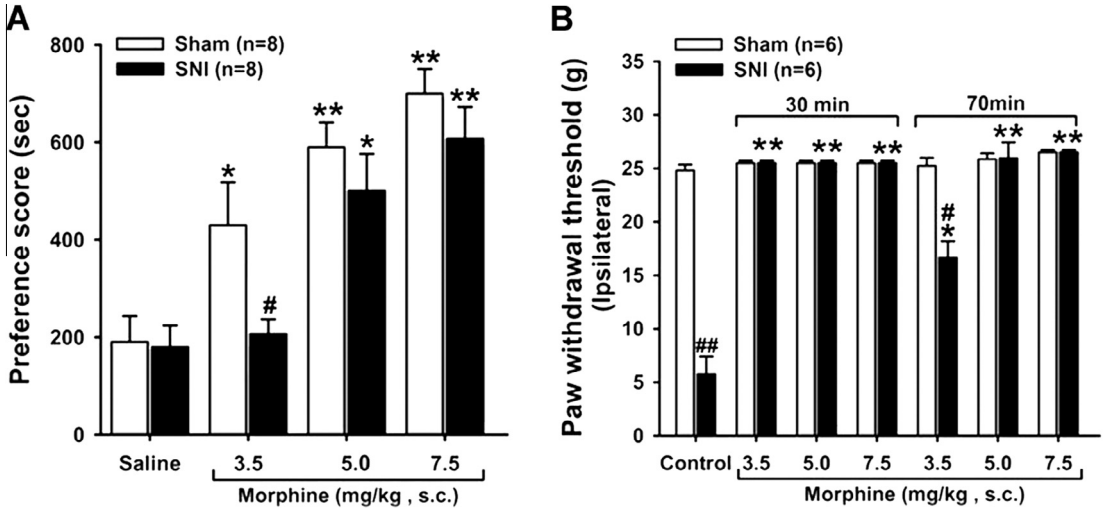

Fig. 2. SNI attenuates CPP and anti-allodynia induced by low dose but not high dose of morphine. (A) The preference scores induced by three dosages of MOR in sham and SNI rats as indicated are shown. (B) The ipsilateral paw withdrawal thresholds in SNI rats were enhanced by the three dosages of morphine at 30 min after application, while at 70 min after 3.5 mg/kg morphine administration the thresholds in SNI rats were lower than those in sham rats but were still higher than those in SNI saline control rats. $^{*}p < 0.05$, $^{**}p < 0.01$ vs saline control; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs sham group.

thresholds in 3.5 mg/kg MOR group decreased significantly, compared with sham group ($p < 0.05$), but were still higher than those in saline control group ($p < 0.05$). The results indicated that MOR at 3.5 mg/kg might depress neuropathic pain but induce no addiction. Therefore, this dose was chosen for following experiments.

3.2. TNF-α is upregulated in NAcc following SNI and the change attenuates MOR-induced CPP

As a previous work has shown that TNF-α prevents METH-induced drug dependence and neurotoxicity [11], we measured the expression of the cytokine in NAcc and VTA with ELISA. The results showed that 7 days after SNI, TNF-α was upregulated in bilateral NAcc ($p < 0.05$), but did not change in bilateral VTA ($p > 0.05$), compared with sham group (Fig. 3A and B). To determine whether the change is responsible for the inhibition of MOR-induced rewarding in SNI rats, we blocked TNF-α by microinjection of anti-TNF-α or IgG (250 ng in 1 μl) into NAcc 2 h before SNI and daily for 12 successive days after SNI (Fig. 1B). As shown in Fig. 3C, in SNI rats treated with 3.5 mg/kg MOR, the preference scores were increased in anti-TNF-α group ($p < 0.05$) but not in IgG group ($p > 0.05$), suggesting that upregulation of TNF-α may be necessary for the depressive effect of SNI on MOR-induced rewarding. To confirm this, we measured the CPP in both wide-type (WT) mice and TNF-α receptor 1 knockout (TNFR1 KO) mice. Similar to the results observed in rats (Fig. 2A), in WT mice MOR at 3.5 mg/kg enhanced preference scores in sham mice ($p < 0.05$) but not in SNI mice ($p > 0.05$), compared with saline controls (Fig. 3D). In TNFR1 KO mice, however, the same dose of MOR induced a significant place preference in SNI group ($p < 0.05$ vs saline control), which was not different from that in sham group ($p > 0.05$) (Fig. 3D). The results indicated that activation of TNFR1 might be essential for suppression of MOR-induced rewarding produced by SNI. To test whether TNF-α is also sufficient for inhibition of CPP, rrTNF-α (1 μg/ml, 1 μl) or aCSF was injected into NAcc or VTA of sham rats during the conditioning phase of CPP tests (Fig. 1A). We found that the preference scores induced by MOR in rats with NAcc injection of rrTNF-α were significantly lower than those treated with aCSF ($p < 0.05$, Fig. 3E) and were not different from those in saline control group ($p > 0.05$, Fig. 3E). In contrast, when the same dose of rrTNF-α was injected into VTA, no difference in the scores between rrTNF-α-treated and aCSF-treated groups was detected ($p > 0.05$, Fig. 3F).

3.3. The upregulation of TNF-α reduces DA level and enhances the dopamine transporter in NAcc

As the dopaminergic system plays an important role in regulation of the rewarding, we examined whether the extracellular DA level in NAcc was changed in SNI rats by using *in vivo* microdialysis technique. Indeed, the DA level in NAcc was markedly decreased on day 7, lasting for at least 28 days following SNI ($p < 0.05$ vs sham

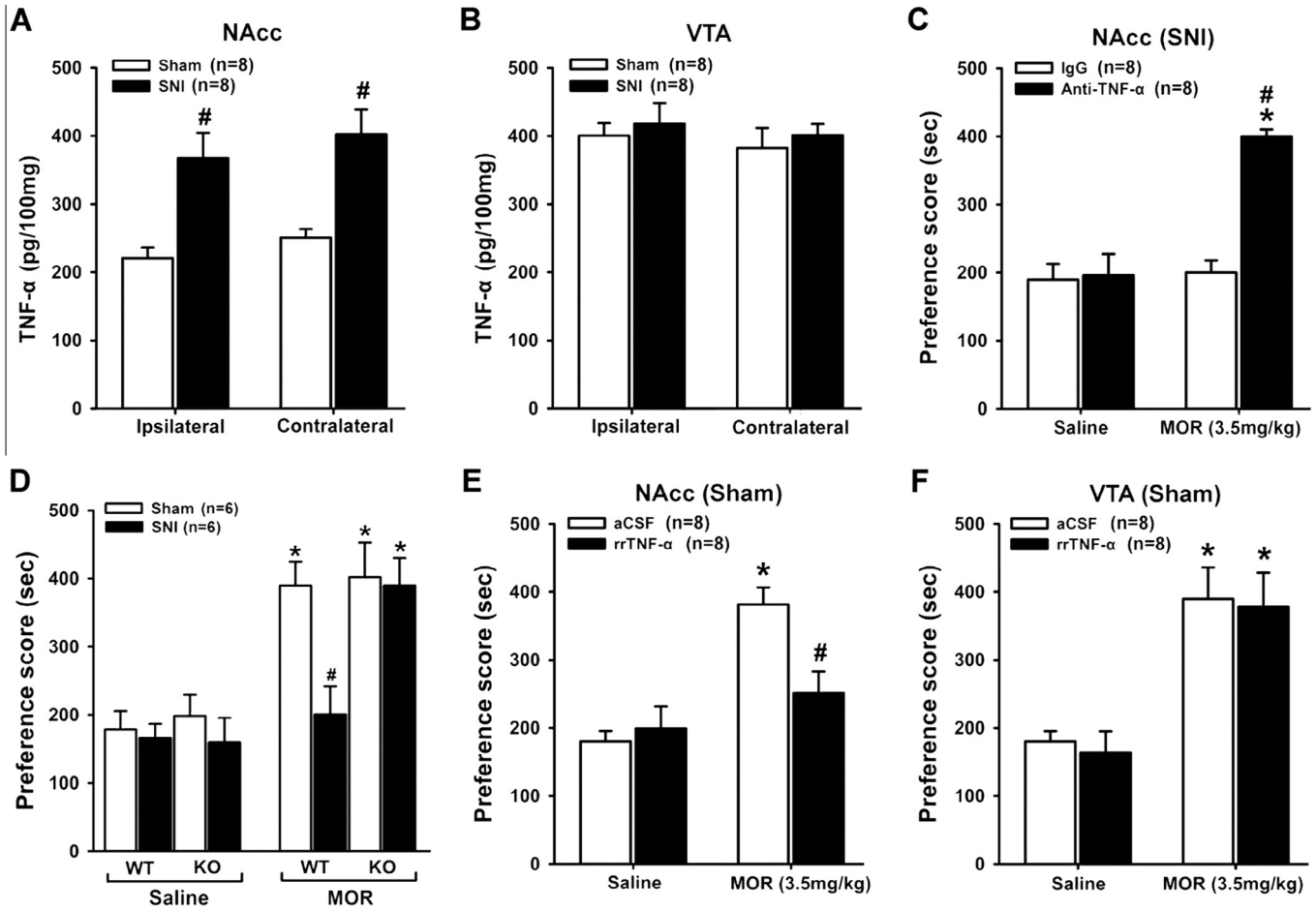

Fig. 3. The upregulation of TNF-α in NAcc suppresses MOR-induced CPP following SNI. (A and B) ELISA revealed that TNF-α is up-regulated in bilateral NAcc but not in VTA on day 7 after SNI. $^{\#}p < 0.05$ vs the sham rats. (C) The effects of microinjection of anti-TNF-α (250 ng in 1 μl) and IgG into NAcc on MOR-induced CPP in SNI rats are shown. $^{\#}p < 0.05$ vs SNI rats with infusion of IgG into NAcc; $^{*}p < 0.05$ vs saline control. (D) SNI suppressed MOR-induced CPP only in WT mice but not in TNFR1 KO mice. $^{*}p < 0.05$ vs saline controls; $^{\#}p < 0.05$ vs WT sham group treated with 3.5 mg/kg MOR. (E) Microinjection of rrTNF-α (1 ng in 1 μl) into NAcc suppressed MOR induced CPP in the sham rats. $^{*}p < 0.05$ vs saline controls, $^{\#}p < 0.05$ vs sham rats with infusion of aCSF. (F) Infusion of rrTNF-α in the same dose into VTA did not change MOR induced CPP in the sham rats. $^{*}p < 0.05$ vs saline controls.

group, Fig. 4A). The decrease in DA level may be resulted from either decreased DA synthesis in VTA or increased DA reuptake in NAcc. Since TH and *p*-TH Ser40, a rate-limiting enzyme of catecholamine biosynthesis [16], are critical for DA synthesis and dopamine transporter (DAT) plays a key role in DA reuptake [17], we measured the protein level of DAT in NAcc and total TH and *p*-TH Ser40 in VTA using western blot method. The results showed that DAT in NAcc was upregulated ($p < 0.01$), but both TH and *p*-TH were not changed in SNI rats ($p > 0.05$), compared to sham rats (Fig. 4B and C). As the upregulation of TNF-α in NAcc may be responsible for suppression of MOR-induced CPP (Fig. 3), we tested if TNF-α is also involved in the upregulation of DAT produced by SNI. As shown in Fig. 4D, microinjection of rrTNF-α into NAcc upregulated DAT in sham rats ($p < 0.01$ vs aCSF control), while injection of anti-TNF-α downregulated DAT in NAcc of the SNI rats ($p < 0.01$ vs IgG control), suggesting that TNF-α is critical for DAT upregulation following SNI. This was further confirmed by the experiments with TNFR1 KO mice. Compared with sham group, significant increase in DAT expression in NAcc was only detected in WT mice ($p < 0.01$) but not in TNFR1 KO mice following SNI ($p > 0.05$, Fig. 4E).

4. Discussion

It has been shown that MOR-induced CPP is reduced in rat model of neuropathic pain [3]. Consistently, early clinical survey studies have suggested that only small part of chronic pain patients exposed to chronic opioid analgesic therapy develop addiction [2,18]. Recent works, however, do not support this notion by showing that around one third of chronic pain patients exposed to longer term opioid develop addiction or pseudo addiction [19,20]. In the present study, we found that the development of MOR-induced CPP in the rats with neuropathic pain depends on the dose of morphine. MOR at 3.5 mg/kg induced CPP only in sham rats but not in SNI rats. When the dose increased to 5 mg/kg, however, MOR also induced CPP in SNI rats. These experimental data suggested that even though neuropathic pain attenuated MOR-induced rewarding, the risk of addiction should not be ignored when prescribing high dose of opioids for maximal pain relief.

It was also debated whether MOR is effective for treating neuropathic pain. A primary clinical study reported that opioid is ineffective for neuropathic and diopathic forms of pain [21]. In contrast, many late studies have demonstrated opioids do relieve

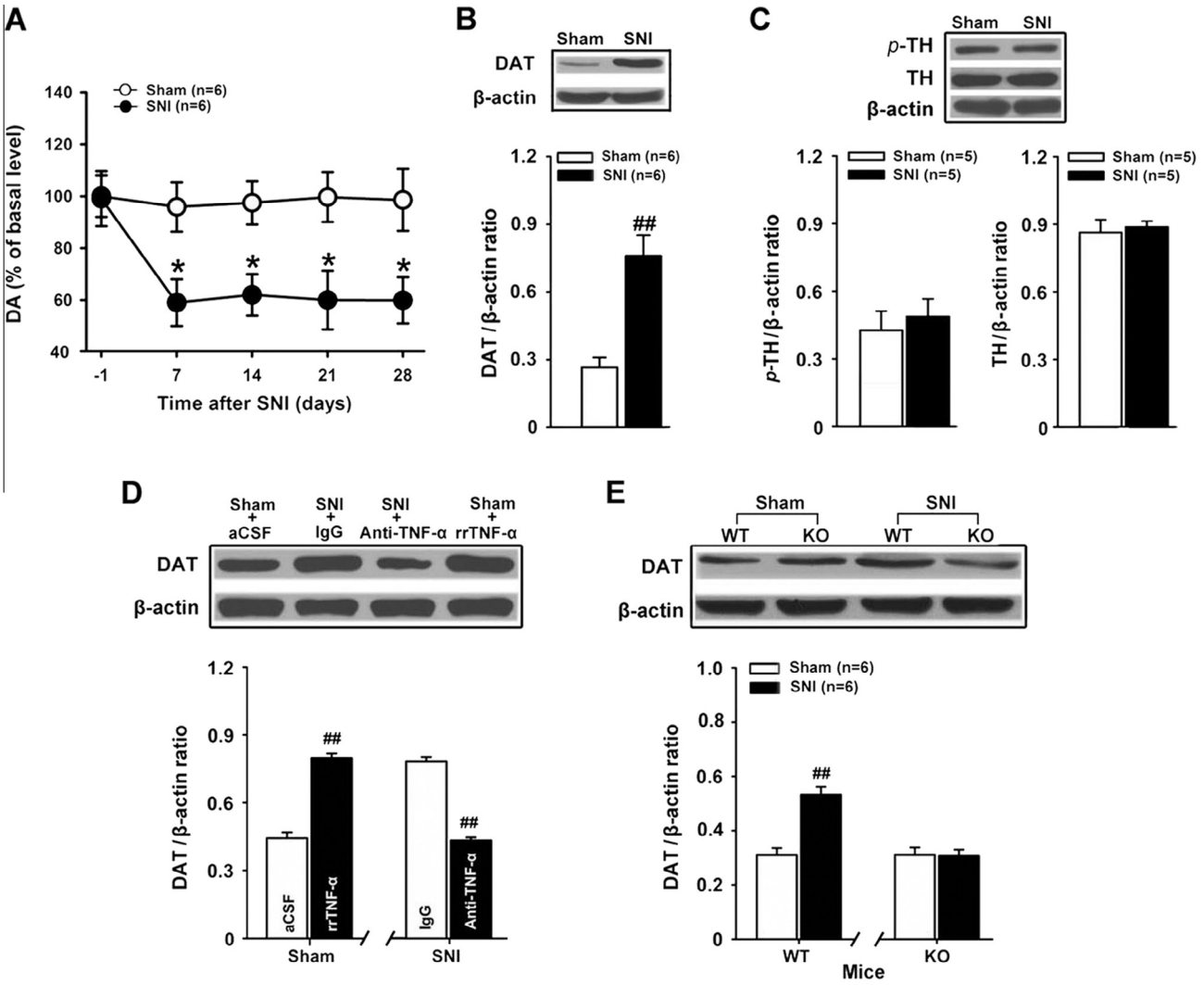

Fig. 4. SNI upregulates DAT in NAcc by upregulation of TNF-α. (A) The changes in DA levels in NAcc of SNI and sham rats are shown. $^{*}p < 0.05$ vs sham group. (B) The western blots showed that the expression of DAT increased in NAcc following SNI. $^{\#\#}p < 0.01$ vs sham control. (C) TH and *p*-TH Ser40 levels in VTA of SNI rats are not different from those of sham group. (D) Intra-NAcc infusion of rrTNF-α increased the expression of DAT in sham rats, while intra-NAcc infusion of anti-TNF-α decreased the expression of DAT in SNI rats. $^{\#\#}p < 0.01$ vs aCSF or IgG group. (E) DAT was upregulated in WT mice but not in TNFR1 KO mice following SNI. $^{\#\#}p < 0.01$ vs sham group.

the neuropathic pain [22]. In the present work, we showed that anti-allodynia effect of MOR at low dose was almost identical to that at high dose within 30 min but the effect was decreased 70 min after application, indicating that the dosage may affect the duration but not the degree of pain relief. If this is true, application of MOR at low dose and in short intervals should get ideal analgesic effect and avoid addiction.

In the present work, we showed at first time that TNF-α was upregulated in NAcc following SNI. The depressive effect of SNI on MOR-induced CPP was blocked by either genetic deletion of TNFR1 or microinjection of anti-TNF-α into NAcc and was mimicked by NAcc injection of rrTNF-α in sham rats. Accordingly, the upregulation of TNF-α in NAcc is not only necessary but also sufficient for the suppression of SNI on MOR-induced rewarding.

How could upregulated TNF-α in NAcc suppress MOR-induced rewarding? It has been well established that DA release in NAcc by activation of VTA is essential for development of addiction [23]. In the present work, we found that the extracellular DA level in NAcc was markedly reduced in SNI rats. As SNI upregulated DAT in NAcc but affected neither total TH nor *p*-TH Ser40 expression in VTA, overexpression of DAT may be responsible for the reduction of DA. Interestingly, the upregulation of DAT in NAcc induced by SNI was again blocked by genetic deletion of TNFR1 or anti-TNF-α and was mimicked by NAcc injection of rrTNF-α in sham animals. Taken together, peripheral nerve injury may suppress the MOR-induced rewarding by upregulation of TNF-α, which reduces DA level in NAcc by upregulation of DAT.

In conclusion, peripheral nerve injury may suppress MOR-induced rewarding by upregulation of DAT via over-production of TNF-α in NAcc.

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