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第四军医大学

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研究生优秀

YANJIUSHENGYOUXIU

论文集

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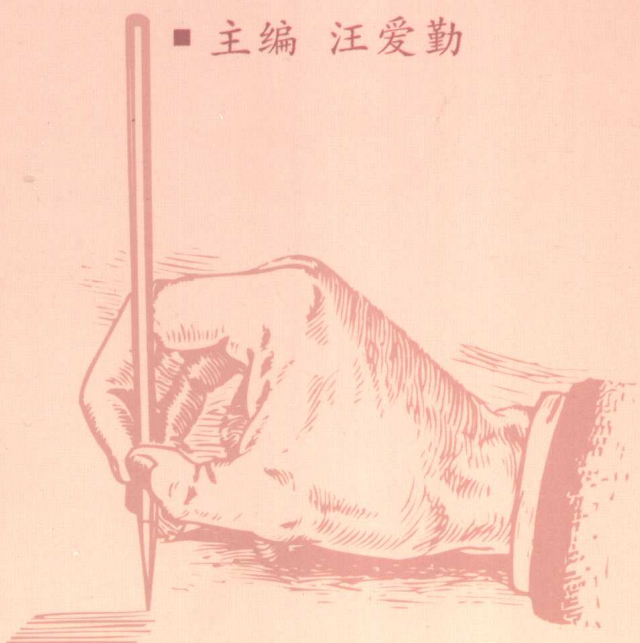
■ 主编 汪爱勤



第四军医大学出版社

第四军医大学

研究生优秀论文集

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前　言

我校研究生教育开展20余年来，为国防医学事业培养了一大批优秀人才，特别是近几年随着学校建设的发展和研究生院的成立，研究生教育的规模和质量都跃上了一个新的台阶。广大研究生已经成为学校教学、医疗、科研的生力军，科研创新能力得到进一步加强，在国内外发表了一批高水平、有一定影响的科研论文。我们对2000年以来我校博士、硕士研究生发表的论文进行了收集与整理，并邀请校内专家教授进行评阅选拔，从几百篇优秀的研究生科研论文中精选出了40篇汇编成册。论文的遴选兼顾了我校医学主干学科、传统优秀学科以及军事医学学科等学科专业的分布，其中大部分被SCI收录，有的发表于《Nucleic Acids Research》等国外著名医学杂志。论文的作者中有全国、全军及陕西省优秀博士论文获得者，有的继续出国深造，有的已经成长为本学科专业的业务骨干，活跃在国防卫生战线的最前沿。这些优秀论文的完成也离不开导师的精心指导。导师中有中国科学院鞠躬院士、工程院樊代明院士和长期从事军事医学研究的郭鹤教授等一大批知名专家教授，通过这些优秀论文也可以反映出他们严谨治学的态度和甘为人梯的精神。

此外，在刚刚结束的“2004全国博士生学术论坛（军队）”活动中，我校7名博士的论文被选为大会交流。大会评出了12篇优秀论文，其中来自我校神经科学研究所的王英鹏同学夺得了医学分论坛惟一的优秀论文奖，我们也在书中对这7篇论文进行了收录。

等闲识得东风面，万紫千红总是春。本书的编撰不应只是对我校研究生教育成果的采撷和展示，更希望能为广大导师和研究生提供一个学习、交流和进步的园地，让今日的姹紫嫣红成为明天的累累硕果。

本书不足及疏漏之处，敬请批评指正。

第四军医大学研究生院院长　汪爱勤教授

2004年12月

Content 目录

2004 全国博士生学术论坛论文

1. Differential Roles of Spinal Neurokinin 1/2 Receptors in Development of Persistent Spontaneous Nociception and Hyperalgesia Induced by Subcutaneous Bee venom Injection in the Conscious Rat

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SUMMARY To evaluate the roles of spinal neurokinin receptors in the development of persistent nociception and hyperalgesia to thermal and mechanical stimuli induced by subcutaneous (s. c.) bee venom injection, effects of intrathecal (i. t.) pre- or post-treatment with a non-selective antagonist of (NK1/2) receptors, [D-Arg1, D-Trp7, 9, Leu11] substance P (spantide), and a selective NK3 receptor antagonist, (S)-(N)-(1-(3-(1-benzoyl-3-(3, 4-dichlorophenyl) piperidin-3-yl) propyl)-4-phenylpiperidin-4-yl)-N-methyl acetamide (SR142801) were assessed in conscious rat. Injection of bee venom s. c. into the plantar surface of one hind paw resulted in a patho logical pain phenomenon characterized by a 1-2 h single phase of persistent spontaneous nociceptive behaviors (continuously flinching the injected paw) and a 72-96 h profound primary thermal and mechanical hyperalgesia in the injection site and a secondary thermal hyperalgesia in the non-injected hindpaw. Pre-treatment with spantide i. t. at 0. 05 mg, 0. 5 mg and 5 mg produced a dose-related suppression of the bee venom-induced flinching reflex during the whole time course and the inhibitory rate was 24 +12. 60% (35. 38 + 4. 12 flinches/5 min, n. 5), 48 +6. 75% (24. 53 +2. 90 flinches/5 min, n. 5) and 60 +7. 69% (18. 88 + 3. 58 flinches/5 min, n. 5) respectively when compared with the saline control group (46. 80 +2. 60 flinches/5 min, n. 5). Post-treatment of spantide i. t. at the highest dose (5 mg) used in the present study 5 min after bee venom injection also produced a 49% suppression of the flinching reflex in the control group [post-spantide vs saline: 19. 42 +3. 15 (n. 5) vs 38. 42 +3. 25 flinches/5 min (n. 5)]. Moreover, i. t. pre-trea tment with 5 mg spantide partially prevented the primary and secondary thermal hyperalgesia from occurring, while it did not show any influence on the development of primary mechanical hyperalgesia. Neither the established thermal nor mechanical hyperalgesia identified in the above sites was affected by i. t. post-treatment with the same dose of spantide 3 h after bee venom injection. Pre and post-treatment of SR142801 did not produce any significant effect on the bee venom-induced spontaneous pain and thermal and mechanical hyperalgesia. Our present result suggests that activation of spinal NK1/2 receptors is involved in both induction and maintenance of the persistent spontaneous nociception, while it is only involved in induction of the primary and secondary thermal, but not primary mechanical hyperalgesia induced by s. c. bee venom injection. The spinal NK3 receptor seems not likely to be involved in the bee venom-induced behavioral response characterized by spontaneous pain and thermal and mechanical hyperalgesia.

INTRODUCTION

Tachykinin has been widely studied as mediators of sensory information and has been found to be involved in various neuronal functions. The tachykinin family includes three subtypes: substance P (SP), neurokinin A (NKA) and neurokinin B

(NKB) with NK1, NK2 and NK3 as their respective preferred receptors (Maggi et al., 1993). SP, a key member of tachykinin family, has been widely accepted as being involved in nociception (Duggan et al., 1988; Laneuville et al., 1988; Linderoth and Brodin, 1988; Kuraishi et al., 1991; Sakurada, 1993; Traub, 1995; De-Felipe et al., 1998; Nichols et al., 1999) by activating at NK1 receptor (Maggi et al., 1993), which located predominantly in the super? cial dorsal horn (Yashpal et al., 1990; Moussaoui et al., 1992). Previous studies have proved that noxious stimulation of the periphery evoked the release of SP into the spinal cord (Duggan et al., 1988; Linderoth and Brodin, 1988) and intrathecal (i.t.) application of SP produces various pain-related behaviors (Hylden and Wilcox, 1983; Laneuville et al., 1988). NK1 receptor antagonists has been found to depress numerous forms of nociceptive behavior such as spontaneous pain induced by subcutaneous (s.c.) formalin and capsaicin (Sakurada et al., 1992; Seguin et al., 1995; Santos and Calixto, 1997) and thermal or mechanical hyperalgesia in mononeuropathic (chronic constriction injury, CCI), diabetic and carrageenan models (Traub, 1995; Coudore-Civiale et al., 1998). In view of the nociception-related functions, NKA was similar to SP in the pattern of distribution and physiological properties (Ogawa et al., 1985; Linderoth and Brodin, 1988; Ma and Woolf, 1995). Behavioral studies also proved a strong involvement of NKA in various pain models (Linderoth and Brodin, 1988; Sakurada et al., 1992; Coudore-Civiale et al., 1998). Along with the distinct distribution of NKB from the other two tachykinins (Ogawa et al., 1985), previous studies on the roles of NKB and NK3 receptor in nociception seem to be multiple and complicated. Intradermal application of selective NK3 receptor antagonist exhibit antinociceptive properties in the capsaicin and formalin test (Sakurada et al., 1992), but was inactive in mononeuropathic and diabetic rats by i.t. application (Coudore-Civiale et al., 1998). Exogenous NKB has been found to exert antinociceptive effect in the spinal cord (Laneuville et al., 1988). However, due to the variety of pain models, we have not got a unanimous view on the role of tachykinins and their receptors in the nociceptive processing. Furthermore, most of the traditional pain models possess only one feature (tonic spontaneous nociception or hyperalgesia) of pathological pain and may not be appropriate to characterize one certain transmitter and its receptor in the whole nociceptive processing which covers variable nociceptive features.

The bee venom model is a newly developed model in evaluating the mechanisms of pathological pain which contains a prolonged, persistent spontaneous pain and primary mechanical and thermal hyperalgesia and secondary thermal hyperlagesia (Chen et al., 1999b). In contrast to the formalin model (a well-known and widely used tonic spontaneous pain model), s.c. injection of bee venom solution into one hindpaw of rats has been demonstrated to be able to produce a prolonged, persistent spontaneous finching reflex, lifting and licking behaviors indicative of pain in a monophasic manner for 1-2 h followed by a profound, persistent primary mechanical and thermal hyperalgesia in the injected hindpaw and a secondary thermal, but not mechanical, hyperalgesia in the uninjected hindpaw (Chen et al., 1999b). Electrophysiological studies performed in cats and rats demonstrated that s.c. bee venom injection could induce a monophasic tonic increased discharges of wide dynamic range (WDR) neurons in the spinal dorsal horn which correlates well with the pattern and duration of the behavioral expressions following the same treatment (Chen et al., 1998; You and Chen, 1999). Our previous studies have also demonstrated that spinal ATP P2x-purinoceptors (Zheng and Chen, 2000) and the peripheral NMDA and non-NMDA receptors (Chen et al, 1999a) are involved in the development of the bee venom-induced persistent spontaneous nociceptive behavioral responses and the increased spike fring of the spinal dorsal horn WDR neurons. Immunohistochemical c-Fos staining showed that the pattern and time course of c-Fos protein expression in the spinal dorsal horn was in parallel with that of the development of hyperalgesia to thermal and mechanical stimuli applied in the injected and the non-injected contralalteral hindpaw (Luo et al., 1998). These features enable this new model to mimick the clinical pathological pain better than other

traditional models. Therefore, the present study was designed to use this novel animal model of pathological pain to further investigate the roles of NK (1/2 and 3) receptors in the development of persistent spontaneous nociception and hyperalgesia to thermal and mechanical stimuli identified in the injection site and the contralateral hind paw.

MATERIALS ANDMETHODS

Experimental animals

The experiments were performed on Sprague – Dawley albino rats weighing from 200 – 260 g. The animals were provided by Laboratory Animal Center of the Fourth Military Medical University (FMMU) and use of the animals was reviewed and approved by the FMMU Animal Care and Use Committee. The IASP' s ethical guidelines for pain research in conscious animals were followed (Zimmermann, 1983). The animals were housed in plastic boxes in group of 3 at 22 – 268C with food and water available ad libitum in the colony room. A 12: 12 h light dark cycle with lights on at 08: 00 was maintained and testing was done between 09: 00 and 18: 30. The rats were acclimatized to the laboratory and habituated to the test boxes for at least 30 min each day for 5 days before testing.

Surgery

Chronic intrathecal catheterization was performed and modified according to a previous report (Yaksh and Rudy, 1976) . Under ketamine anesthesia (50 mg/kg, i. p.), a 2cm long skin incision was carried out and muscles were separated from C7 – T4 vertebrae. A laminectomy was performed in T2 or T3 and the dura was opened. To prevent the inset tubing from moving, a PE – 8 tube (0. 2mm i. d., 0. 5mm o. d.) was initially passed through a 1cm long muscle tunnel and then advanced caudally (3 – 5cm distance between the entry and the target level) through the subarachnoid space to the rostral level of the lumbar enlargement (i. e. the caudal tip of the catheter ended between spinal levels L3 and L4). Finally, the outer end of the PE – 8 tubing was firmly fixed by sewing the free end of the medical – use tape, which had been stuck tightly on the outer end of the tube, to the paravertebral muscles. The wound was washed with sterile saline and treated with antibiotics and the muscles and skin sutured by layers. The whole operation was performed under strictly sterile conditions. Rats showing any neurological defcits postoperatively were sacrificed. After tests, each animal was checked for the position of the inner end of the tube, those with it in the wrong position place or local pathological change were also abandoned.

Administration of drugs

Spantide (Sigma) and SR142801 (Sanofi Recherche, France) was dissolved in 0. 9% sterile saline and dimethyl sulfoxide (DMSO) respectively and was diluted to working concentration according to previous reports and our pilot experiment. Bee venom was lyophilized whole venom of Apis millifera (Sigma, St. Louis, MO) dissolved in 0. 9% sterile saline. A volume of 0. 05 ml saline containing 0. 2mg lyophilized whole venom was used during the whole experiment according to our previous research (Chen et al, 1998; Luo et al, 1998; Chen et al., 1999a, b; You and Chen, 1999). Application of the drugs was performed i. t. by a 25 ml microsyringe containing 5 ml spantide (containing 0. 05 mg, 0. 5 mg or 5 mg) or SR142801 solution (containing 40 or 65 mg) or 5 m1 vehicle (saline or DMSO), followed by a flush with 9 ml saline. To examine the possible roles of NK1/2 and NK3 receptors in the induction and maintenance of the bee venom – induced persistent spontaneous pain and hyperalgesia, the effects of i. t. pre – or posttreatment with the drugs and vehicles were observed respectively (Fig. 1).

Assessment of the spontaneous pain – related behaviors and mechanical and thermal hyperalgesia

The procedures for assessment of the persistent spontaneous nociceptive behaviors and hyperalgesia to mechanical and thermal stimuli were described detailedly in our previous report (Chen et al., 1999b, Zheng and Chen, 2000) . A 303030cm transparent plexiglas test box with a transparent glass floor was placed on a supporting frame of 30cm high above the experimental table to allow the experimenters to observe the paws of the animals without obstruction. The rat was placed in the test box for at least 30 min before administration of the bee venom and the other drugs. The spontaneous nociceptive behavior was determined by counting the number of flinches of

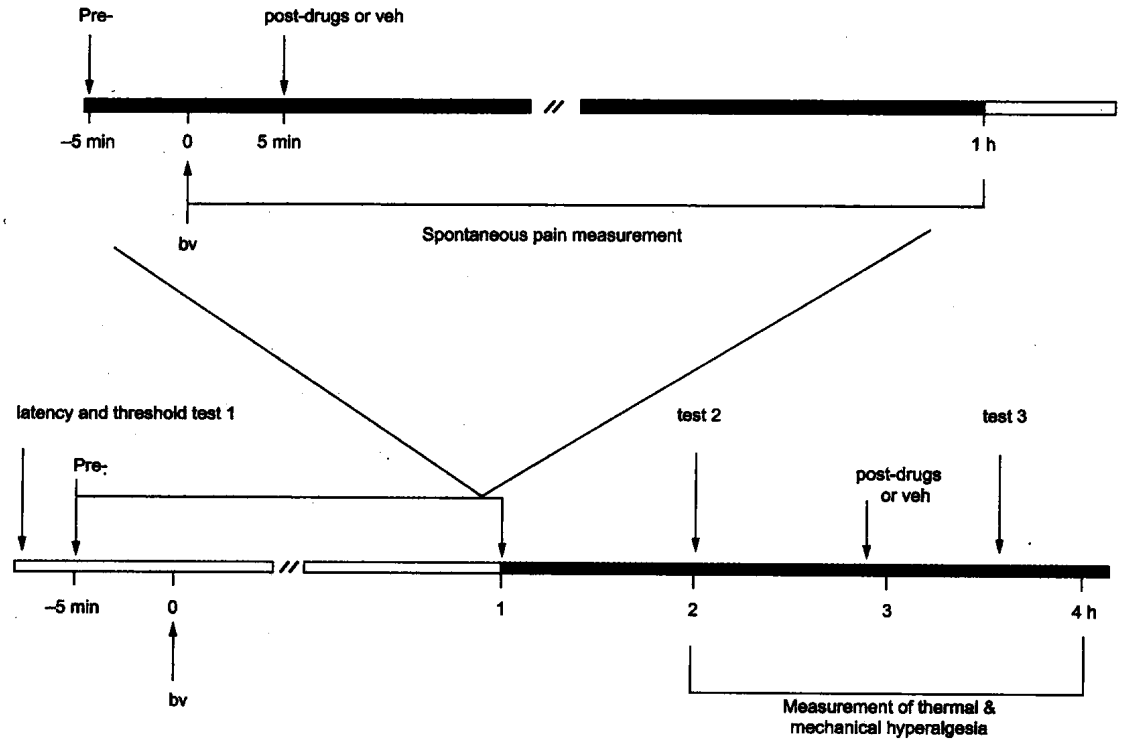

Fig. 1 The diagram showing the protocols of administration of vehicles (vel) and NK receptors antagonists and measurement of the bee venom (bv) – induced persistent spontaneous nociception and hyperalgesia to thermal and mechanical stimuli applied in the injected and the non – injected pawpads. The drugs were administered 5 min prior to (arrow for pre –) or 5 min after (arrow for post –) s. c. bv for assessment of the effect on induction and maintenance of spontaneous pain (upper panel), while the drugs were administered 5 min prior to or 170 min after s. c. bv for assessment of the effect on induction and maintenance of thermal and mechanical hyperalgesia (lower panel). Latency and threshold test 1, test 2 and test 3 indicate the timing when measurement was started for values of normal, post – bv (2 h) and post – drugs (3 – 4 h). Arrows for bv indicate starting time of injection.

each 5 min interval following bee venom injection.

Mechanical stimuli were applied with 3 sets of serial size in diameter of 0. 205, 0. 235, and 0. 5mm thick von Freytype nylon filaments with bending force ranging from 3. 92 – 105, 9. 8 – 392, and 39. 2 – 588 mN. The rat was placed on a metal mesh floor covered with a plexiglas chamber (202025 cm) and von Frey filaments were applied from underneath the metal mesh floor to the plantar surface of the bilateral hindpaws. A von Frey filament was applied 10 times (several seconds for each stimuli) to each testing area. The bending force of the von Frey filament being able to evoke 50% occurrence frequency of paw withdrawal was expressed as the mechanical threshold.

To examine thermal hyperalgesia, the rats were placed on the surface of a 2mmthick glass plate covered with the same plexiglas chamber to measure the sensitivity to heat stimuli with a RTY – 3 radiant heat stimulator (Xi' an Fenglan Instrumental Factory, P. R. China) . The radiant heat source was a high intensity halogen lamp bulb (100W) positioned under the glass floor directly beneath targeting area on the hind paw. The distance between the projector lamp bulb and lower surface of the glass floor was adjusted to produce a light spot on the ? oor surface 5mm diameter.

The heat stimuli were directed onto the injected area and the symmetrical site on the contralateral hind paw of each rat under the voltage of 10 V. The tests were performed alternately on each hind paw. Four stimuli were repeated for each site and the inter – stimulus interval was more than 10 min for the same site and 5 min for the different sites. The latency was determined as the duration from the beginning of thermal stimuli to the occurrence of hind

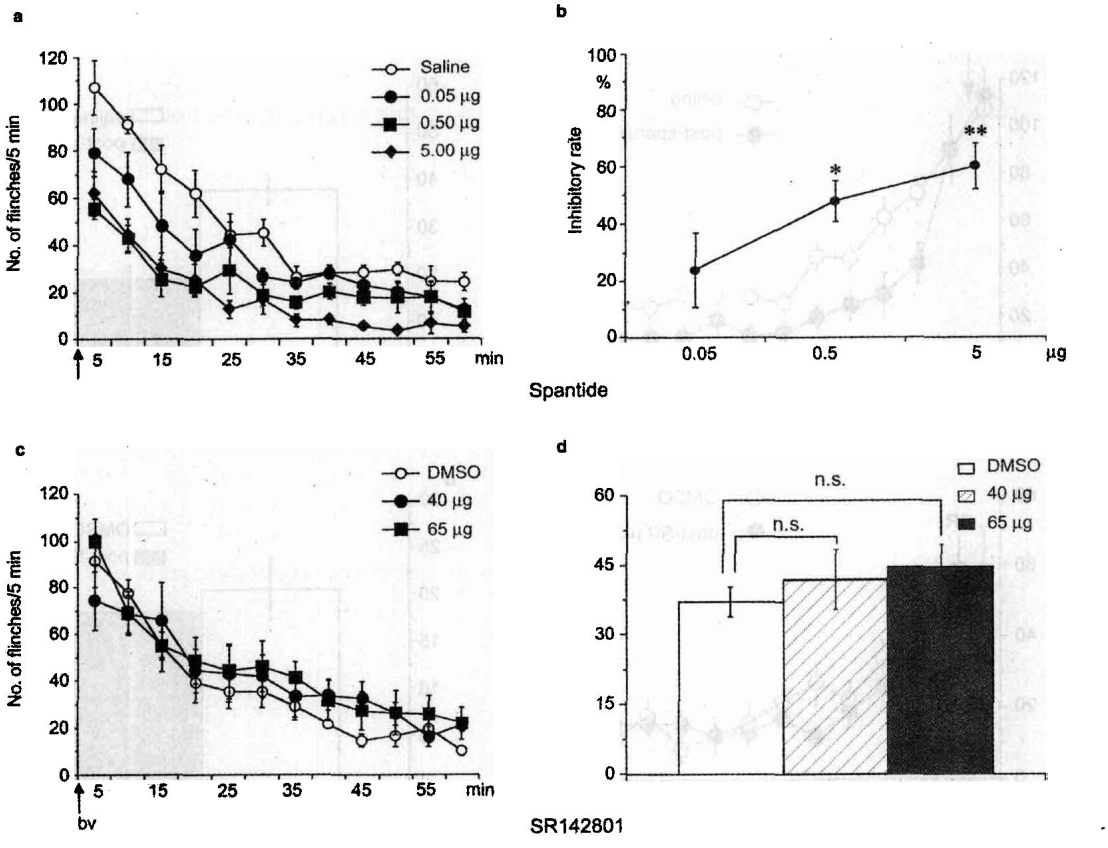

Fig. 2 Effects of i. t. pre – treatment of spantide and SR142801 on the persistent spontaneous nociception induced by s. c. bee venom (bv) injection. Curve graph (a) shows the mean time courses and (b) shows the inhibitory rates of i. t. pre – treatment of three doses of spantide (0. 05, 0. 5 and 5 mg) on the mean numbers of flinching reflex per 5 min averaged from 12 time blocks of 1 h compared with i. t. pre – saline treatment. Curve graph (c) shows the mean time courses and column graph (d) shows the mean numbers of flinching reflex per 5 min averaged from 12 time blocks of 1 h after i. t. treatment of two doses of SR142801 (40 and 65 mg) and DMSO. * *, $P < 0.01$; *, $P < 0.05$; n. s., no significant; Vertical bars: + SEM.

paw withdrawal reflex.

Data analysis

All data were expressed as mean + SEM. Non – parametric Mann – Whitney U – test was used for comparative analysis of the flinching number in 1 h time course of the vehicle and drug – treated groups and ANOVA (Fisher' s post hoc) was used for the analysis of changes in mechanical or thermal sensitivity of both hind paws prior to and after bee venom, and prior to and after administration of drugs and vehicles. P value < 0. 05 was considered to be statistically significant.

RESULTS

Every experimental animal used in the behavioral observation showed no signs of neurological dysfunction such as muscle trembling or motor weakness caused by i. t. application of spantide and SR142801. Similar to our previous report (Chen et al., 1999b), s. c. bee venom injection into the plantar surface of one hindpaw of conscious rats produced not only an early phase of persistent spontaneous flinching reflex (1 – 2 h) (Figs. 2a, c and 3a, c), but also a late phase of dramatical reduction in mechanical threshold and thermal latency identified in the injection site (primary hyperalgesia) and a reduction in thermal latency, but not mechanical threshold, in the noninjected contralateral hindpaw (secondary hyperalgesia) (Figs. 4 – 7). The peak time of development of primary thermal and mechanical hyperalgesia and secondary thermal hyperalgesia was between 2 – 8 h after bee venom

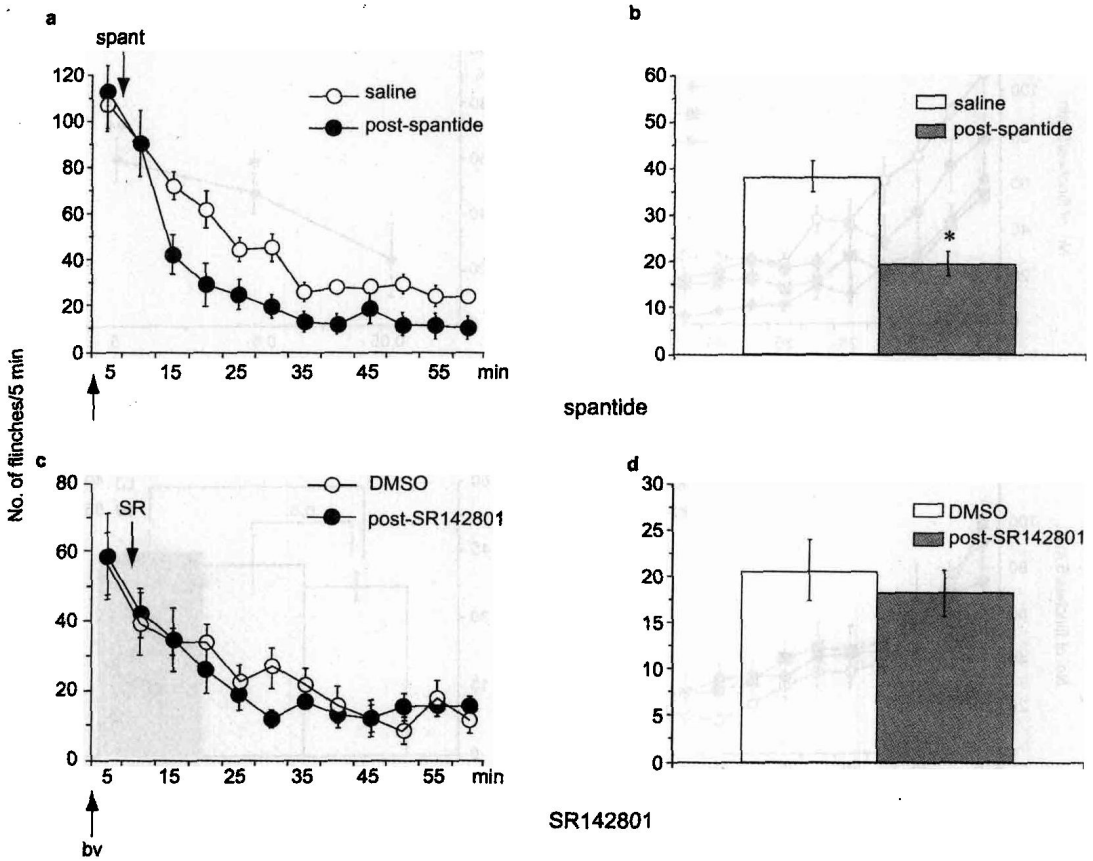

Fig. 3 Effects of i. t. post – treatment of spantide and SR142801 on the established persistent spontaneous nociception induced by s. c. beevenom (bv) injection. Curve graph (a) shows the mean time courses and column graph (b) shows the mean numbers of flinching reflex per 5 min averaged from 10 time blocks of the later 50 min after i. t. spantide (span, 5 mg) and saline. Curve graph (c) shows the mean time courses and column graph (d) showing the mean numbers of flinching reflex per 5 min averaged from 10 time blocks of 50 min after i. t. SR142801 (SR, 40 mg) and DMSO. *, P <0.05; Vertical bars: +SEM.

treatment, which was also consistent with our previous report (Chen et al., 1999b).

Effects of i. t. NK receptor antagonists on persistent spontaneous pain

Fig. 2a shows the mean time courses of the effects of i. t. pre – treatment with saline and three doses of spantide at 0. 05 mg, 0. 5 mg and 5 mg on the bee venom – induced persistent flinching reflex. Pre – treatment with i. t. spantide resulted in a dose – dependent suppression of the flinching reflex when compared with i. t. saline pre – treated group over 1 h time course observation. As shown in Fig. 2b the inhibitory rate for the three doses of spantide was 24 + 12. 60% (35. 38 + 4. 12 flinches/5 min, n. 5; P > 0. 05), 48 + 6. 75% (24. 53 + 2. 90 flinches/5 min, n. 5; P < 0. 05) and 60 + 7. 69% (18. 88 + 3. 58 flinches/5 min, n. 5; P < 0. 01) respectively compared with the control group (46. 80 + 2. 60 flinches/5 min, n. 5) . Post – treatment with i. t. spantide at 5 mg 5 min after s. c. bee venom also produced a significant inhibition of the flinching reflex of the control group by 49% (post – spantide vs saline: 19. 42 + 3. 15 9 vs 38. 42 + 3. 25 flinches / 5 min, n. 5 for each group; P < 0. 05) in the subsequent 50 min time course after spantide (Fig. 3a and b) . Statistical comparative analysis showed no significant difference in inhibition of the flinchingnumberbetween pre – andpost – treatment of spantide at dose of 5 mg [pre – vs post – treatment: 12. 04 + 3. 00 (n. 5) vs 19. 42 + 3. 15 flinches/5 min (n = 5), P > 0. 05].

Fig. 2c shows the mean time courses of the effects of i. t. pre – treatment with DMSO – saline mixture and two doses of SR142801 at 40 and 65

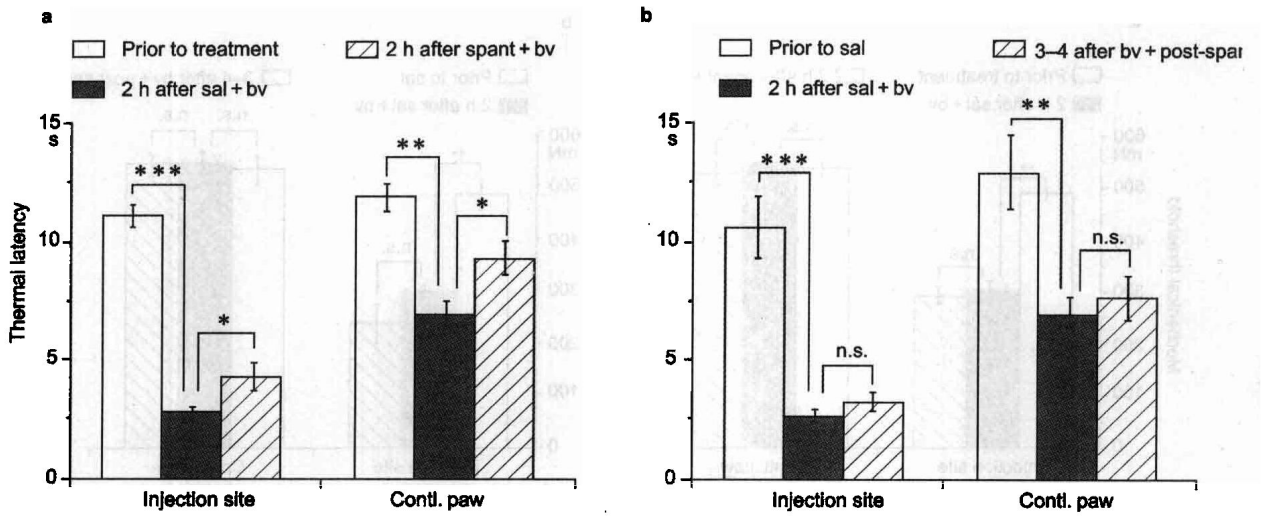

Fig. 4 Effects of i. t. pre – (a) and post – treatment (b) with spantide (span) on induction and maintenance of the bee venom (bv) – induced primary (Injection site) and secondary (Contl. paw, non – injected pawpad) thermal hyperalgesia. In both a and b, the thermal latency was significantly decreased when tested in the injection site and the Contl. paw 2 h after saline (filled column: 2 h after sal. bv) compared with the values prior to any treatment (open column). Pre – treatment of spantide (5 mg) produced a partial inhibitory effect on the primary and secondary thermal hyperalgesia (a, hatched column: 2 h after spant. bv). Post – treatment of spantide (5 mg) did not affect established thermal hyperalgesia identified in either injection site or Contl. paw 3 – 4 h after bv (b, hatched column: 3 – 4 h after bv. post – spant). ***, $P < 0.001$; **, $P < 0.01$; *, $P < 0.05$; n. s., no significant; Vertical bars: + SEM.

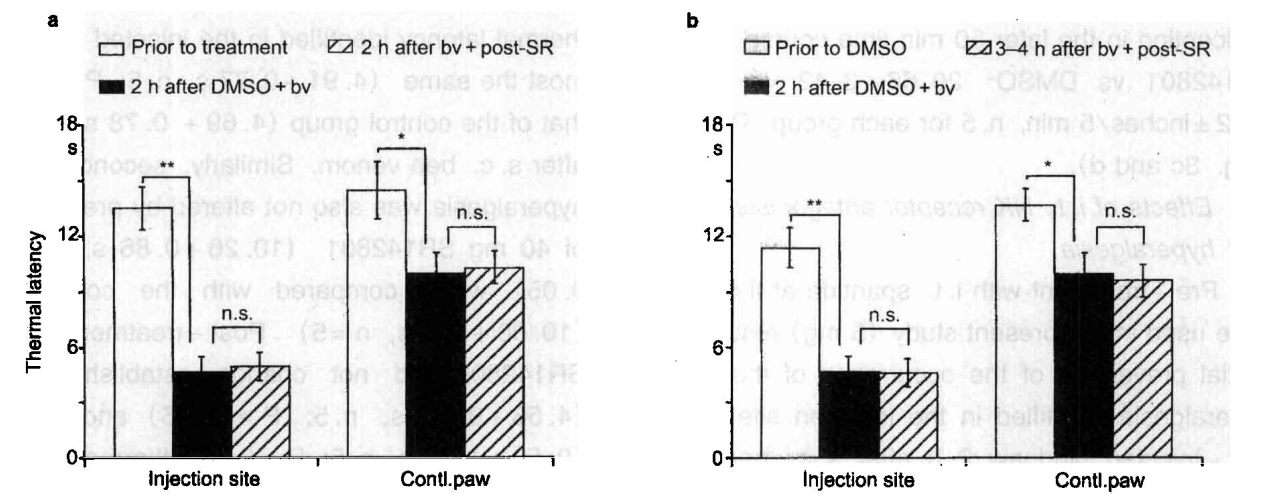

Fig. 5 Effects of i. t. pre – (a) and post – treatment (b) with SR142801 (SR) on induction and maintenance of the bee venom (bv) – induced primary (Injection site) and secondary (Contl. paw, non – injected pawpad) thermal hyperalgesia. In both a and b, the thermal latency was significantly decreased when tested in the injection site and the Contl. paw 2 h after DMSO (filled column, 2 h after DMSO. bv) compared with the values prior to any treatment (open column). Neither pre – (a) nor post – treatment (b) of SR (40 mg) produced any significant influence upon the development of thermal hyperalgesia identified in the injection site and the Contl. paw (hatched column: 2 h after SR. bv for a, 3 – 4 h after bv. post – SR for b). **, $P < 0.01$; *, $P < 0.05$; n. s., no significant; Vertical bars: + SEM.

mg on the bee venom – induced persistent flinching reflex. There is no significant difference in the mean total numbers of flinches, as shown in Fig. 2d, between the two doses of SR142801 – treated group (41.88 + 6.55 and 44.78 + 4.85 flinches/5 min, n. 5 for each group; $P > 0.05$) and control group (37.05 + 3.14 flinches/5 min, n = 5). Post – treatment of 40 mg SR1428015 min after bee venom also

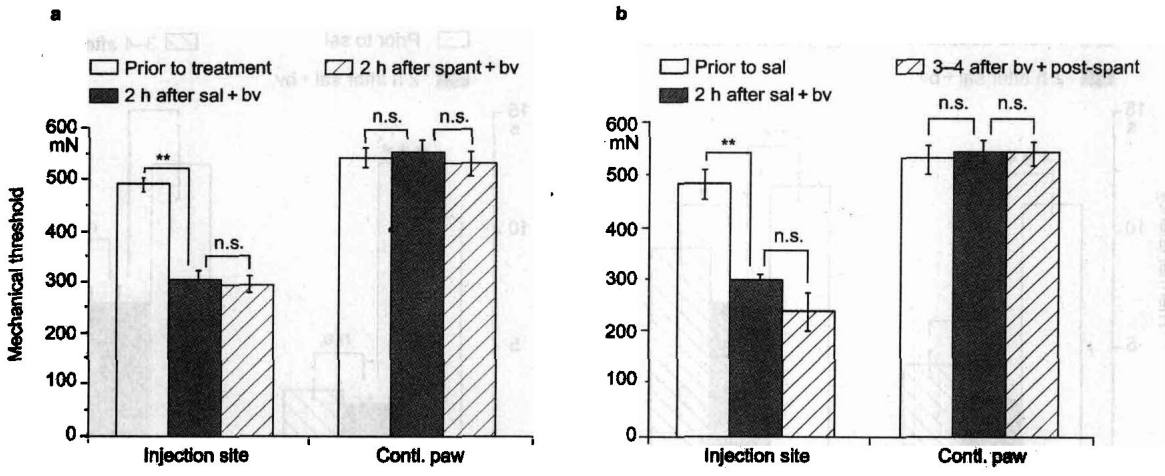

Fig. 6 Effects of i. t. pre – (a) and post – treatment (b) with spantide (spant) on induction and maintenance of the bee venom (bv) – induced primary mechanical hyperalgesia. In a and b, s. c. bv only produced a significant mechanical hyperalgesia in the injection site, but not in the non – injected hindpaw (Contl. paw) tested 2 h after saline (2 h after sal. bv) treatment (filled column) when compared with the values prior to treatment (open column). Neither i. t. pre – (a) nor post – treatment (b) with spant influenced the development of mechanical hyperalgesia induced by s. c. bv (hatched column: 2 h after spant. bv for a, 3 – 4 h after bv. post – spant for b). * *, $P < 0.01$; n. s., no significant; Vertical bars: + SEM.

failed to produce any influence on the spontaneous nociception in the later 50 min time course (post – SR142801 vs DMSO: 20.66 + 3.42 vs 18.36 + 2.42 ± inches/5 min, n. 5 for each group; $P > 0.05$) (Fig. 3c and d).

Effects of i. t. NK receptor antagonists on thermal hyperalgesia

Pre – treatment with i. t. spantide at the highest dose used in the present study (5 mg) resulted in a partial prevention of the occurrence of the thermal hyperalgesia identifled in the injection site and the non – injected hindpaw 2 h after s. c. bee venom (Fig. 4a). However, i. t. post – treatment with the same dose of spantide failed to produce signifIcant influence upon the established primary and secondary thermal hyperalgesia (Fig. 4b). The thermal latency in the injection site was increased by 37% (pre – spantide vs pre – saline: 4.39 + 0.59 s vs 2.77 + 0.27 s, n. 5; $P < 0.05$), while that in the non – injected hindpaw was increased by 25% (pre – spantide vs pre – saline: 9.49 + 0.76 s vs 7.10 + 0.53 s, n. 5; $P < 0.05$) following i. t. pre – treatment of spantide.

Pre – treatment of i. t. SR142801 at 40 mg failed to produce any influence on primary and secondary thermal hyperalgesia. As shown in Fig. 5a thermal latency identifled in the injected site was almost the same (4.91 + 0.77 s, n. 5; $P > 0.05$) as that of the control group (4.69 + 0.78 s, n = 5) 2 h after s. c. bee venom. Similarly, secondary thermal hyperalgesia was also not altered by pre – treatment of 40 mg SR142801 (10.26 + 0.86 s, n = 5; $P > 0.05$) when compared with the control group (10.00 + 1.1 s, n = 5). Post – treatment of 40 mg SR142801 did not change established primary (4.56 + 0.62 s, n. 5; $P > 0.05$) and secondary (9.59 + 1.19 s, n. 5; $P > 0.05$) thermal hyperalgesia identi – fled during 3 – 4 h after bee venom injection when compared with the value obtained 2 h after bee venom treatment (Fig 5b 4.69 + 0.78 s and 10.00 + 1.10 s for primary and secondary thermal hyperalgesia, n = 5).

Effects of i. t. NK receptor antagonists on mechanical hyperalgesia

Neither pre – nor post – treatment with i. t. spantide at 5μg produced any influence upon the development of primary mechanical hyperalgesia identified in the injection site was dropped by 39% in the pre – saline treated group (303 ± 17.84mN, n = 5), 40% in the pre-spantide treated group (294 +