Anti-nociceptive role of neuropeptide Y in the nucleus accumbens in rats with inflammation, an effect modulated by mu- and kappa-opioid receptors*

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Abstract Recent study in our laboratory showed that neuropeptide Y (NPY) plays an antinociceptive role in the nucleus accumbens (NAc) in intact rats. The present study was performed to further investigate the effect of NPY in nociceptive modulation in the NAc of rats with inflammation, and the possible interaction between NPY and the opioid systems. Experimental inflammation was induced by subcutaneous injection of carrageenan into the left hindpaw of rats. Intra-NAc administration of NPY induced a dose-dependent increase of hindpaw withdrawal latencies (HWLs) to thermal and mechanical stimulations in rats with inflammation. The anti-nociceptive effect of NPY was significantly blocked by subsequent intra-NAc injection of the Y1 receptor antagonist NPY28-36, suggesting an involvement of Y1 receptor in the NPY-induced anti-nociception. Furthermore, intra-NAc administration of the opioid antagonist naloxone significantly antagonized the increased HWLs induced by preceding intra-NAc injection of NPY, suggesting an involvement of the endogenous opioid system in the NPY-induced anti-nociception in the NAc during inflammation. Moreover, the NPY-induced anti-nociception was attenuated by following intra-NAc injection of the μ-opioid antagonist β-funaltrexamine (β-FNA), and κ-opioid antagonist nor-binaltorphimine (nor-BNI), but not by δ-opioid antagonist naltrindole, indicating that μ- and κ-opioid receptors, not δ-opioid receptor, are involved in the NPY-induced anti-nociception in the NAc in rats with inflammation.

Keywords: nucleus accumbens, neuropeptide Y, Y1 receptor, carrageenan; anti-nociception, μ- and κ-opioid receptors.

Neuropeptide Y (NPY), one of the most abundant neuropeptides in the nervous system, mediates its diverse physiological functions through activation of specific G-protein-coupled receptors[1,2]. Of the multifold biological functions of NPY playing in the central nervous system (CNS), the role of NPY in nociceptive modulation has been studied widely as it has been demonstrated to be involved in pain processing in the CNS[3—6]. The work in our laboratory has proved that the latency of nociceptive response increased dose-dependently after intra-nucleus raphe magnus (intra-NRM) and intra-periaqueductal grey (intra-PAG) administration of NPY[7—9]. Recently, a close relationship between NPY and inflammation in the CNS has been implicated. Behavioral studies have shown that NPY may be involved in the transmission of nociceptive information in the spinal cord in rats with inflammatory pain[10—12]. Nevertheless, the mechanisms of the anti-nociceptive effects of NPY on inflammation, especially in rat brain, are not yet clearly known.

It has been reported that the anxiolytic effects produced by intra-cerebroventricular injection of NPY could be blocked by naloxone, suggesting that there is an interaction of NPY system with opioid system in the CNS[13]. Recent studies in our laboratory showed that the anti-nociception induced by intra-PAG injection of NPY was reversed by naloxone in both intact rats and rats with inflammation[7,8]. Also, the NPY-induced anti-nociceptive effect in the NRM was reversed by naloxone[9]. Moreover, our previous study found that the anti-nociceptive effect of NPY in the NAc was also modulated by activation of opioid system in intact rats[14]. Together, opioid system plays an important role in the physiological effect of NPY in the brain.

It is well known that the nucleus accumbens (NAc) is a limbic structure of brain and plays an important role in the supraspinal endogenous opioid-modulated nociceptive processing[15,16]. Furthermore, previous studies reported that the NAc plays an important role in mediating the suppression of tonic or persistent pain[17,18]. Results in our laboratory have

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shown that intra-NAc administration of NPY resulted in dose-dependent anti-nociception in intact rats[14]. This agrees with the histological localization of NPY and its receptors in this region[1,2,19,20].

Carrageenan-induced inflammation is a commonly used model for the study of pain and it is useful to assess the NPY-induced anti-nociceptive effect in rats with inflammation[8]. Thus, the present study was performed to investigate the nociceptive role of NPY in the NAc in rats with inflammation. Furthermore, we also investigated the possible involvement of opioid receptors in the NPY-induced anti-nociception.

1 Materials and methods

1.1 Animal preparation

Experiments were carried out on freely moving male Wistar rats weighting 220—250 g (Experimental Animal Center of Academy of Military Medical Sciences, Beijing, China). The rats were housed in cages with free access to food and water, and maintained at room temperature of 24 ± 2 ℃ with a normal day/night cycle. All experiments were conducted according to the guidelines of the International Association for the Study of Pain[21] and every effort was made to minimize animal suffering and the number of animal used.

1.2 Nociceptive tests

The hindpaw withdrawal latencies (HWLs) during thermal and mechanical stimulation were measured[22,23]. Briefly, the entire ventral surface of the rat hindpaw was placed manually on a hot plate, which was maintained at temperature of 52 ℃ (51.8—52.4 ℃). The time to hindpaw withdrawal was measured in seconds and referred to as the HWL to thermal stimulation. The Randall Selitto Test (Ugo Basile, Type 7200, Italy) was used to assess the HWL to mechanical stimulation. A wedge-shaped pusher at a loading rate of 30 g/s was applied to the dorsal surface of the manually handled hindpaw and the latency required to initiate the withdrawal response was assessed and expressed in seconds. The value of the HWL obtained before intra-NAc injection was regarded as the basal HWL. The HWL recorded during subsequent measurements (measured at 5, 10, 20, 30 and 60 min after intra-NAc injection) was expressed as percentage changes of the basal level for each rat (% change of the HWL). Each rat was tested with both types of stimulation. A cut-off limit of 15 s was set up to avoid tissue damage. All rats were accustomed to the testing conditions for five days before the starting of the experiment to minimize the stress induced by handling.

1.3 Carrageenan-induced inflammation

Carrageenan-induced inflammation is a widely used model that can closely reproduce some human pain syndromes[24], thus the same model was used in the present study. Animals received a unilateral injection of carrageenan (2 mg in 0.1 mL saline; Sigma, St. Louis, USA) into the left hindpaw, and the contralateral paw was untreated. Three hours after injection of carrageenan, the HWL was measured by the Hotplate Test and the Randall Selitto Test. Then each animal received an intra-NAc injection of either vehicle or drug, and the HWLs of each animal were thereafter assessed.

1.4 Intra-NAc microinjection

The animals were anaesthetized by intraperitoneal sodium pentobarbital (50 mg/kg) and were mounted on a stereotaxic instrument. A stainless steel guide cannula (20 gauge) was positioned 1.0 mm dorsally to NAc (B + 1.7, L 1.8, V 6.0 mm from the surface of the skull; B, Bregma; L, lateral to midline; V, ventral to the surface of skull) according to Paxinos and Watson[25] and was fixed to the skull by dental acrylic. On the experimentation day a stainless steel needle (26 gauge) was directly inserted into the guide cannula, with 1.0 mm beyond the tip of the guide cannula. One microliter of solution was thereafter infused into the NAc over one minute, and the injection needle was left in the place for 30 s after each injection.

1.5 Chemicals

Solutions for intra-NAc injection were prepared with sterilized saline (0.9%), each with a volume of 1 μL of: (1) 0.1, 0.5 or 1 mmol/L of NPY (human neuropeptide Y, Sigma Chemical Co., St. Louis, USA); (2) 0.1, 0.5 or 1 mmol/L of NPY28-36 ((Pro30, Try32, Leu34) NPY28-36, Neosystem Laboratories, France); (3) 7.5, 15 or 30 μg of naloxone (naloxone hydrochloride, Sigma Chemical Co., St. Louis, USA.); (4) 0.1, 1 or 5 mmol/L of β-funaltrexamine (β-FNA hydrochloride, Tocris Cookson Ltd., Bristol, UK); (5) 0.1, 1 or 5 mmol/L of nor-binaltorphimine (nor-BNI dihydrochloride, Tocris Cookson Ltd.); (6) 5 mmol/L of

naltrindole (naltrindole hydrochloride, Tocris Cookson Ltd.).

1.6 Statistical analysis

At the end of the experiments, the location of the tip of the injection tube was verified. Only the results from nociceptive tests where the tips of the injection tube were within the NAc were used for statistical analysis. Data from nociceptive tests were presented as mean ± SEM. The difference between groups was determined by the two-way analysis of variance (ANOVA). $^{*}P<0.05$, $^{**}P<0.01$ and $^{***}P<0.001$ were considered as significant differences.

2 Results

2.1 Effects of intra-NAc administration of NPY on the HWLs to thermal and mechanical stimulation

To test whether NPY plays an anti-nociceptive role in the NAc in rats with inflammation, rats received intra-NAc injection of 1 μL of 0.1 ($n=6$), 0.5 ($n=8$) or 1.0 mmol/L of NPY ($n=8$), or 1 μL of 0.9% saline as a control ($n=6$). As shown in Fig. 1, the HWLs to thermal and mechanical stimulations increased significantly after intra-NAc injection of 0.5 (Thermal test: $F_{left/left}=5.76$, $P<0.05$; $F_{right/right}=2.27$, $P=0.15$. Randall Selitto test: $F_{left/left}=12.16$, $P<0.01$; $F_{right/right}=2.49$, $P=0.13$) or 1.0 mmol/L of NPY (Thermal test: $F_{left/left}=12.25$, $P<0.01$; $F_{right/right}=11.61$, $P<0.01$. Randall Selitto test: $F_{left/left}=39.65$, $P<0.001$; $F_{right/right}=51.66$, $P<0.001$), but not 0.1 mmol/L of NPY (Thermal test: $F_{left/left}=0.18$, $P=0.67$; $F_{right/right}=0.02$, $P=0.89$; Randall Selitto test: $F_{left/left}=0.01$, $P=0.92$; $F_{right/right}=1.43$, $P=0.25$), compared with the control group. The anti-nociceptive effect of NPY reached the peak 10 to 20 min after intra-NAc administration of NPY and then recovered at 30 min, as shown in Fig. 1. The results suggest that NPY exerts anti-nociceptive effects in the NAc of rats with inflammation.

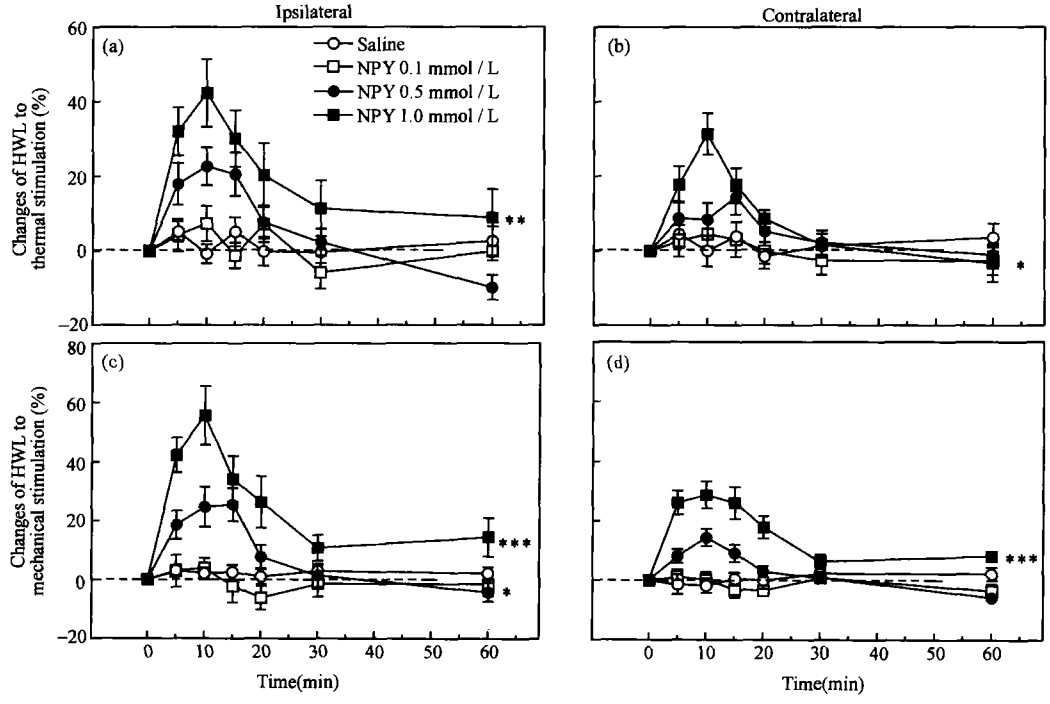

Fig. 1. Effects of intra-NAc administration of NPY on HWLs to thermal (a) and (b) and mechanical stimulation (c) and (d) in rats with inflammation. Data are presented as mean ± SEM. $^{*}P<0.05$, $^{**}P<0.01$ and $^{***}P<0.001$ compared with the control group.

2.2 Involvement of Y1 receptor in the NPY-induced anti-nociception in the NAc

A previous study demonstrated that the Y1 receptor plays an important role in the NPY-induced anti-nociception[2]. To test whether the Y1 receptors are involved in the NPY-induced anti-nociception in the NAc in rats with inflammation, the Y1 receptor antagonist NPY28-36 was used. Rats received intra-NAc injection of 1 μL of 1.0 mmol/L of NPY, followed 5 min later by intra-NAc injection of 0.1 ($n=7$), 0.5 ($n=7$), 1 mmol/L ($n=7$) of NPY28-36,

or 1 μL of 0.9% saline as a control ($n = 15$). The results are shown in Fig. 2. The HWLs to both thermal and mechanical stimulations increased after intra-NAc injection of NPY. Compared with the control group, the increased HWLs were blocked significantly by subsequent intra-NAc injection of 0.5 (Thermal test: $F_{left/left} = 3.27$, $P = 0.09$; $F_{right/right} = 4.81$, $P < 0.05$. Randall Selitto test: $F_{left/left} = 3.81$, $P = 0.06$; $F_{right/right} = 2.88$, $P = 0.14$), or 1.0 mmol/L of NPY28-36 (Thermal test: $F_{left/left} = 7.56$, $P < 0.05$; $F_{right/right} = 10.66$, $P < 0.01$. Randall Selitto test: $F_{left/left} = 9.69$, $P < 0.01$; $F_{right/right} = 9.36$, $P < 0.01$), but not by 0.1 mmol/L of NPY28-36 (Thermal test: $F_{left/left} = 2.02$, $P = 0.17$; $F_{right/right} = 1.62$, $P = 0.21$. Randall Selitto test: $F_{left/left} = 0.35$, $P = 0.56$; $F_{right/right} = 0.24$, $P = 0.62$). Another group of rats ($n = 8$) received intra-NAc injection of 1 μL of saline, followed 5 min later by intra-NAc injection of 1 mmol/L of NPY28-36. There were no significant changes in HWLs during 60 min after the injection, as shown in Fig. 2. The results indicate that Y1 receptor is involved in the anti-nociceptive effect of NPY in the NAc of rats with inflammation.

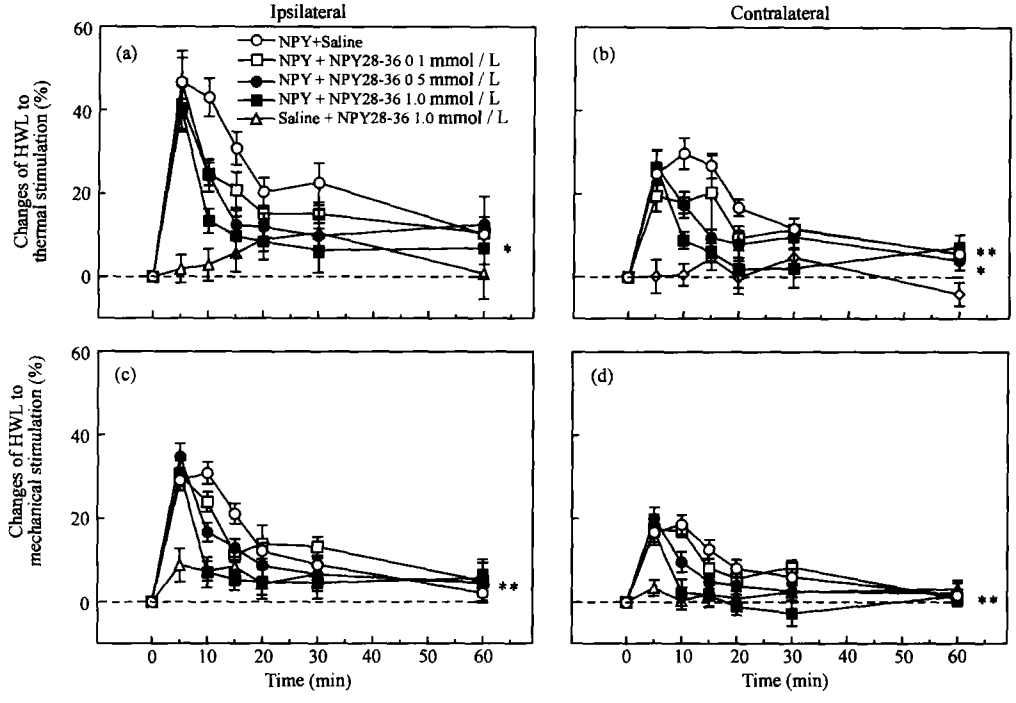

Fig. 2. Effects of intra-NAc administration of NPY28-36 on the NPY-induced increases in HWLs to thermal (a) and (b) and mechanical (c) and (d) stimulations in rats with inflammation. Data are presented as mean ± SEM. Only the data measured at 10, 15, 20, 30 and 60 min were taken for two-way ANOVA. $^{*}P < 0.05$ and $^{**}P < 0.01$ compared with the control group.

2.3 Involvement of opioid receptors in the NPY-induced anti-nociception in the NAc

To test whether the opioid receptors are involved in the anti-nociceptive effect of NPY in the NAc of the rats with inflammation, we employed the broad-spectrum opiate antagonist, naloxone. Four groups of rats received intra-NAc injection of 1 μL of 1 mmol/L of NPY, followed 5 min later by intra-NAc injection of 7.5 ($n = 6$), 15 ($n = 10$) or 30 μg ($n = 6$) of naloxone, or 1 μL of 0.9% saline as a control ($n = 15$). As shown in Fig. 3, the HWL to both thermal and mechanical stimulations increased after intra-NAc injection of NPY. The increased HWLs to thermal and mechanical stimulation were attenuated significantly after intra-NAc injection of 15 (Thermal test: $F_{left/left} = 10.68$, $P < 0.01$; $F_{right/right} = 12.27$, $P < 0.01$. Randall Selitto test: $F_{left/left} = 2.12$, $P = 0.15$; $F_{right/right} = 2.26$, $P = 0.14$) or 30 μg of naloxone (Thermal test: $F_{left/left} = 8.72$, $P < 0.01$; $F_{right/right} = 9.16$, $P < 0.01$. Randall Selitto test: $F_{left/left} = 5.92$, $P < 0.05$; $F_{right/right} = 5.16$, $P < 0.05$), but not 7.5 μg of naloxone (Thermal test: $F_{left/left} = 1.30$, $P = 0.26$; $F_{right/right} = 1.23$, $P = 0.27$. Randall Selitto test: $F_{left/left} = 2.35$, $P = 0.14$; $F_{right/right} = 0.82$, $P = 0.37$) compared with the control group. Another group of rats received in-

tra-NAc injection of 1 μL of saline, followed 5 min later by intra-NAc injection of 30 μg of naloxone ($n = 8$). There were no significant changes in HWLs during 60 min after the injection, as shown in Fig. 3. The results prove that opioid receptors are involved in the anti-nociceptive effect of NPY in the NAc of rats with inflammation.

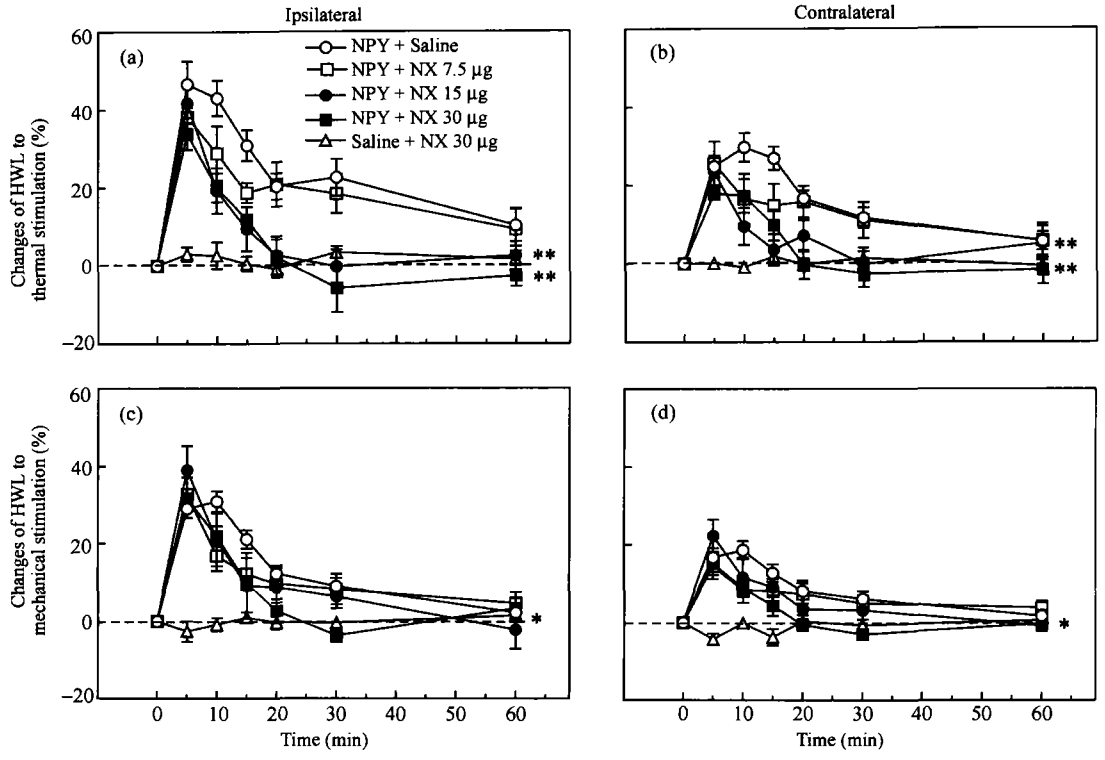

Fig. 3. Effects of intra-NAc administration of naloxone (NX) on the NPY-induced increases in HWLs to thermal (a) and (b) and mechanical stimulation (c) and (d) in rats with inflammation. Data are presented as mean ± SEM. Only the data measured at 10, 15, 20, 30 and 60 min were taken for two-way ANOVA. $^{*}P<0.05$ and $^{**}P<0.01$ compared with the control group.

2.4 Influence of intra-NAc injection of β-FNA on the NPY-induced anti-nociception

Selective antagonists of different opioid receptors were employed to determine which of the three classical opioid receptors was involved in the NPY-induced anti-nociception in the NAc of the rats with inflammation.

First, the μ-opioid receptor antagonist β-FNA was used. Rats received intra-NAc injection of 1 μL of 1.0 mmol/L of NPY, followed 5 min later by intra-NAc injection of 0.1 ($n = 5$), 1 ($n = 9$) or 5 mmol/L of β-FNA ($n = 6$), or 1 μL of 0.9% saline as a control ($n = 15$). The results are shown in Fig. 4. After intra-NAc injection of NPY the HWLs to both thermal and mechanical stimulation increased. Compared with the control group, the NPY-induced increases in HWLs were attenuated significantly by intra-NAc injection of 1.0 (Thermal test: $F_{left/left} = 3.46$, $P = 0.07$; $F_{right/right} = 5.97$, $P < 0.05$. Randall Selitto test: $F_{left/left} = 0.04$, $P = 0.83$; $F_{right/right} = 2.05$, $P = 0.17$) or 5.0 mmol/L of β-FNA (Thermal test: $F_{left/left} = 9.89$, $P < 0.01$; $F_{right/right} = 1.09$, $P = 0.31$. Randall Selitto test: $F_{left/left} = 13.03$, $P < 0.01$; $F_{right/right} = 4.48$, $P < 0.05$), but not by 0.1 mmol/L β-FNA (Thermal test: $F_{left/left} = 1.12$, $P = 0.30$; $F_{right/right} = 0.08$, $P = 0.78$. Randall Selitto test: $F_{left/left} = 1.52$, $P = 0.23$; $F_{right/right} = 1.61$, $P = 0.22$). Another group of rats received intra-NAc injection of 1 μL of 0.9% saline, followed 5 min later by intra-NAc injection of 5 mmol/L of β-FNA ($n = 8$). There were no significant changes in HWLs during 60 min after the injection, as shown in Fig. 4. The results demonstrated that μ-opioid receptor is involved in the anti-nociceptive effect of NPY in the NAc of rats with inflammation.

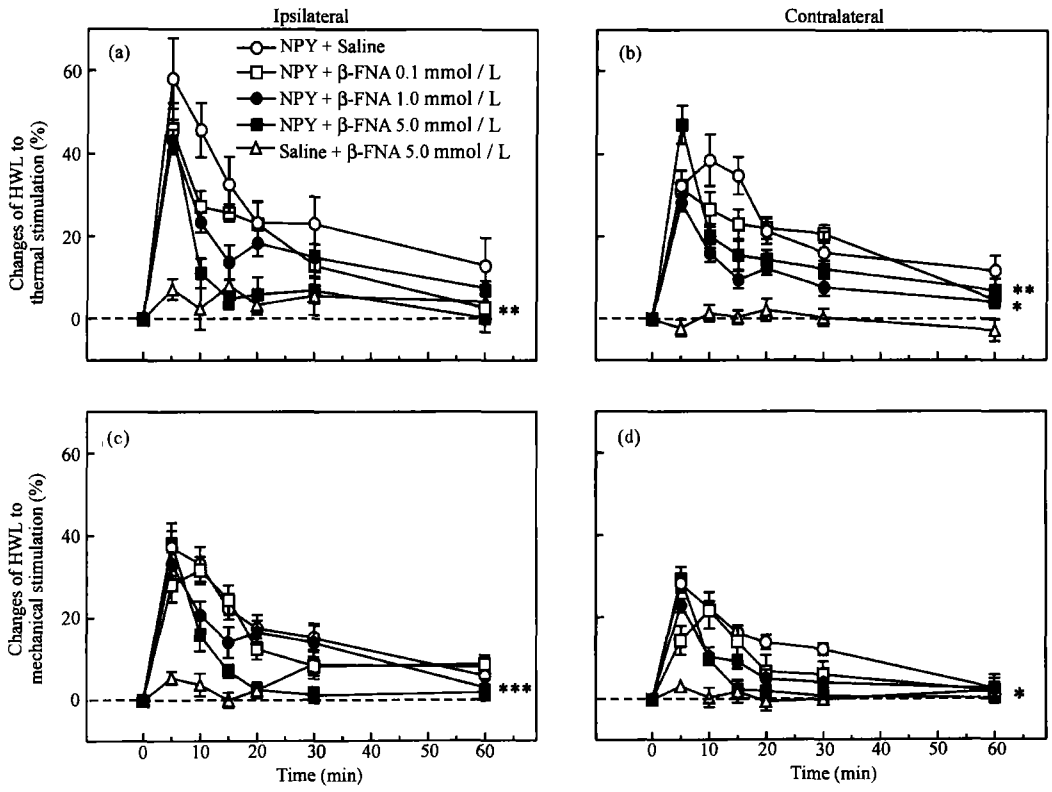

Fig. 4. Effects of intra-NAc administration of β-FNA on the NPY-induced increases in HWLs to thermal (a) and (b) and mechanical stimulation (c) and (d) in rats with inflammation. Data are presented as mean ± SEM. Only the data measured at 10, 15, 20, 30 and 60 min were taken for two-way ANOVA. $^{*}P<0.05$ and $^{**}P<0.01$ compared with the control group.

2.5 Influence of intra-NAc injection of nor-BNI on the NPY-induced anti-nociception

Secondly, the κ-opioid receptor antagonist nor-BNI was used. Rats received intra-NAc injection of 1 mmol/L NPY, followed 5 min later by intra-NAc injection of 0.1 ($n=8$), 1 ($n=8$) or 5 mmol/L of nor-BNI ($n=8$), or 1 μL 0.9% saline as a control ($n=15$). Fig. 5 shows the experimental results. After intra-NAc injection of NPY the HWLs to both thermal and mechanical stimulation increased. Compared with the control group, the NPY-induced increase of the HWL was attenuated significantly by the intra-NAc injection of 1.0 (Thermal test: $F_{left/left}=2.31$, $P=0.14$; $F_{right/right}=4.72$, $P<0.05$. Randall Selitto test: $F_{left/left}=2.91$, $P=0.11$; $F_{right/right}=2.98$, $P=0.98$) or 5.0 mmol/L nor-BNI (Thermal test: $F_{left/left}=6.07$, $P<0.05$; $F_{right/right}=17.52$, $P<0.001$. Randall Selitto test: $F_{left/left}=14.69$, $P<0.001$; $F_{right/right}=8.46$, $P<0.01$), but not by 0.1 mmol/L nor-BNI (Thermal test: $F_{left/left}=0.56$, $P=0.45$; $F_{right/right}=1.26$, $P=0.27$. Randall Selitto test: $F_{left/left}=0.51$, $P=0.48$; $F_{right/right}=0.98$, $P=0.33$). Another group of rats ($n=8$) received intra-NAc injection of 1 μL saline, followed 5 min later by intra-NAc injection of 5.0 mmol/L nor-BNI. There were no significant changes in HWLs during 60 min after the injection, as shown in Fig. 5. The results indicate that κ-opioid receptor is involved in the anti-nociceptive effect of NPY in the NAc of the rats with inflammation.

2.6 Influence of intra-NAc injection of naltraindole on the NPY-induced anti-nociception

Thirdly, the δ-opioid receptor antagonist naltrindole was used. Rats received intra-NAc injection of 1 μL of 1.0 mmol/L of NPY, followed 5 min later by intra-NAc injection of 5.0 mmol/L of naltrindole ($n=8$), or 1 μl of 0.9% saline as a control ($n=15$). After intra-NAc injection of NPY the HWLs to both thermal and mechanical stimulation increased. Compared with the control group, there were no significant changes in HWLs after intra-NAc injection of naltrindole (Thermal test: $F_{left/left}=0.02$, $P=0.87$; $F_{right/right}=0.38$, $P=0.54$. Randall Selitto test: $F_{left/left}=1.62$, $P=0.21$; $F_{right/right}=1.67$, $P=0.21$), as shown in Fig. 6. The results suggest that δ-opioid receptor is not involved in the anti-nocicep-

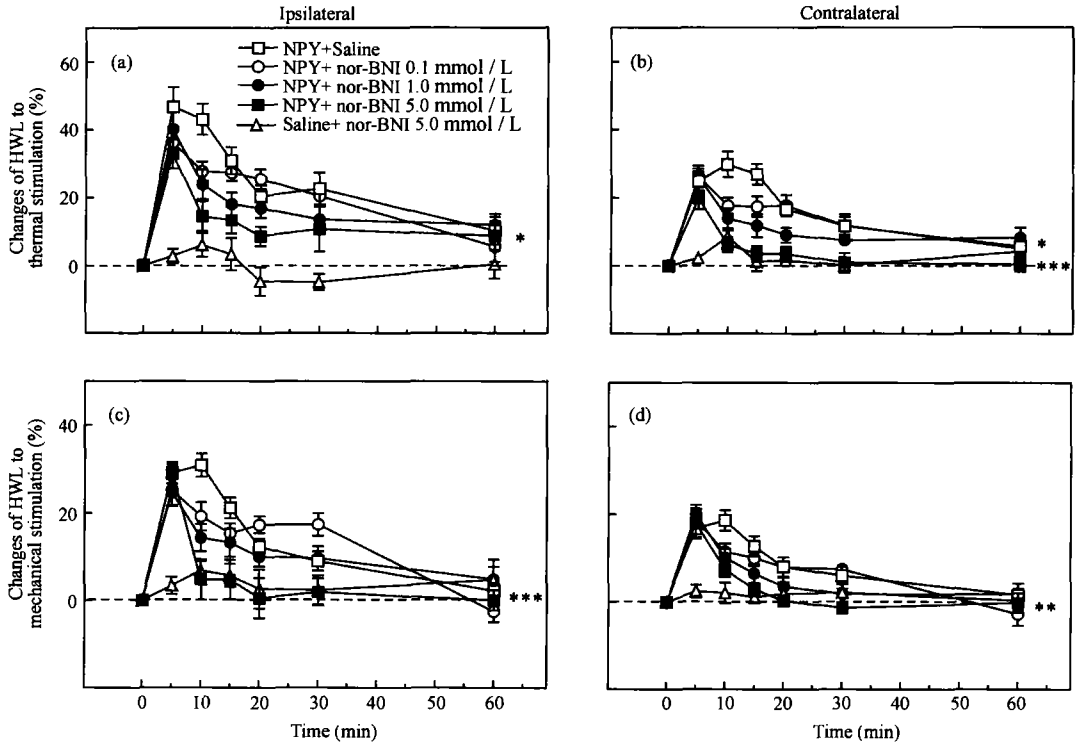

Fig. 5. Effects of intra-NAc administration of nor-BNI on the NPY-induced increases in HWLs to thermal (a) and (b) and mechanical stimulation (c) and (d) in rats with inflammation. Data are presented as mean ± SEM. Only the data measured at 10, 15, 20, 30 and 60 min were taken for two-way ANOVA. $^{*}P<0.05$, $^{**}P<0.01$ and $^{***}P<0.001$ compared with the control group.

tive effect of NPY in the NAc of rats with inflammation.

3 Discussion

The present study demonstrated that intra-NAc administration of NPY induced a dose-dependent increase of HWLs to both thermal and mechanical stimulation in rats with inflammation, indicating that NPY produces an anti-nociceptive effect in the NAc during inflammation. The NPY-induced anti-nociception was subsequently blocked by following intra-NAc injection of the Y1 receptor antagonist NPY28-36, illustrating that this effect is mediated by the Y1 receptor. Furthermore, the anti-nociceptive effect of NPY could be attenuated by intra-NAc administration of the opioid antagonist naloxone, suggesting an interaction between endogenous opioids and NPY in the modulation of nociception in the NAc of the rats with inflammation. In this study, the NPY-induced anti-nociception was attenuated by intra-NAc injection of the selective opioid antagonists β-FNA and nor-BNI, but not by naltrindole, indicating that μ- and κ-opioid receptors, not the δ-opioid receptor, are involved in the NPY-induced anti-nociception in the NAc of rats with inflammation.

The effect of NPY on the nociceptive modulation during inflammation has been implicated in several studies[12,26]. A recent study showed that intrathecal injection of NPY induced a dose-dependent anti-nociceptive effect in carrageenan-induced inflammation[12]. In support of the role of NPY in inflammatory pain are the findings that intrathecal administration of NPY produced an inhibitory effect on the flexor reflex in rats with inflammation[26], implicating an anti-nociceptive role of NPY in nociceptive modulation. Furthermore, it has been proved that there is a plasticity of NPY in the spinal cord during inflammation[10]. This agrees with the anti-nociceptive role of endogenous NPY at the spinal level[12]. The present study found that intra-NAc microinjection of NPY induced significant increase in HWLs to noxious stimulation in rats with inflammation, suggesting that NPY plays an anti-nociceptive effect in the NAc of the rats with inflammation. Combining with our previous results that demonstrated an anti-nociceptive role of NPY in the NAc, this study provides the evidence for that the NAc is one of the important regions where NPY exhibits its anti-nociceptive roles in the brain.

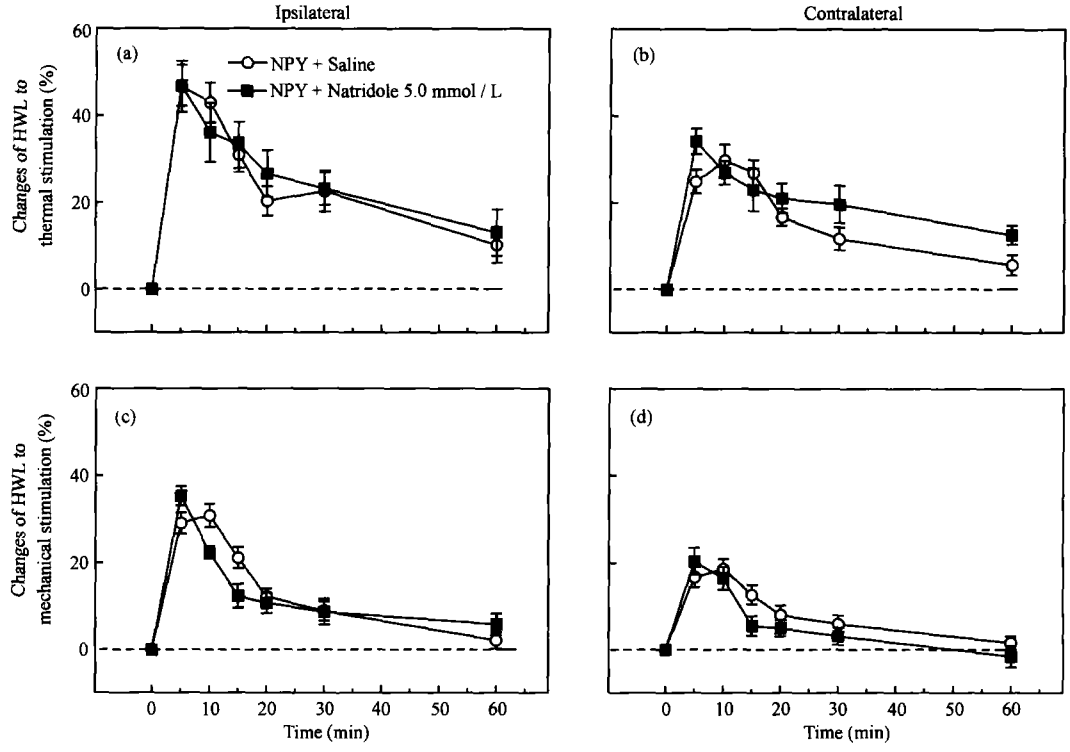

Fig. 6. Effects of intra-NAc injection of naltrindole on the NPY-induced increases in HWLs to thermal (a) and (b) and mechanical stimulation (c) and (d) in rats with inflammation. Data are presented as mean ± SEM. Only the data measured at 10, 15, 20, 30 and 60 min were taken for two-way ANOVA.

Our finding that the NPY-induced anti-nociception could be attenuated by the Y1 receptor antagonist NPY28-36 in a dose-dependent manner, implicating that the NPY-induced anti-nociception is mediated by the Y1 receptor. This is consistent with our previous studies which demonstrated that Y1 receptor plays an important role in the NPY-induced anti-nociception in several important structures of rat brain[7,8,9,14], including rats with carrageenan-induced inflammatory pain[8]. Taiwo and Taylor[12] also reported that following intrathecal administration of NPY, subsequent intrathecal administration of Y1 receptor antagonist BIBO 3304 could partly reverse the NPY-induced anti-nociception in rats associated with intraplantar formalin injection, this supports further that Y1 receptors are involved in the NPY-induced anti-nociceptive responses in rats with inflammation. Furthermore, BIBO 3304 could also reverse the inhibitory effect of NPY on thermal hypersensitivity in the complete Freund's adjuvant model, indicating a contribution of spinal Y1 receptors to NPY anti-hyperalgesia during inflammation[12,27].

Our present study showed that the anti-nociceptive effect of NPY induced by intra-NAc administration was attenuated by the subsequent injection of naloxone, suggesting an involvement of endogenous opioid system in the NPY-induced anti-nociception in the NAc of the rats with inflammation. It is well known that the NAc is one of the few regions with high concentrations of all three types of opioid receptors. Receptor autoradiographic and mRNA gene expression studies have verified that μ-, κ- and δ-opioid receptors can be found in the NAc[28]. In order to determine which type of opioid receptor is involved in the anti-nociceptive effect of NPY in the NAc, the selective opioid antagonists were used. We found that intra-NAc administration of 5.0 mmol/L of μ-opioid receptor antagonist β-FNA and 5.0 mmol/L of κ-opioid antagonist nor-BNI attenuated the NPY-induced anti-nociception in the NAc of rats with inflammation, while intra-NAc administration of 5.0 mmol/L of δ-opioid antagonist naltrindole did not influence the NPY-induced anti-nociception in rats with carrageenan-induced inflammation, illustrating that μ- and κ-opioid receptors, not δ-opioid receptor, are involved in the NPY-induced anti-nociception in the NAc of the rats with inflammation. Taken together, it is possible that NPY may activate opioid system to inhibit the transmission of nociceptive information in the NAc.

It has been suggested that the NAc interacts with both ascending nociceptive processing and descending nociceptive modulation[18,29]. The descending control of pain modulated by NAc is mainly through the well-known PAG-raphe ventral medulla-spinal cord pathway[18]. Also, Yu and Han[15,30] have reported that opioids play an anti-nociceptive role through activation of the pathway from the NAc to the PAG. Gear and Levine[29] also reported that there was a direct ascending projection from the spinal cord to the NAc, in which the opioid system was involved to exert a tonic inhibitory role in the nociceptive transmission. Moreover, the present study found that the anti-nociceptive effect induced by intra-NAc administration of NPY was reduced by subsequent injection of different opioid antagonists, suggesting an involvement of endogenous opioids in the NPY-induced anti-nociception[14]. Thus, it is quiet possible that NPY functions through the opioid system directly or indirectly in the NAc to activate the descending pathways and/or inhibit the ascending pathway to induce anti-nociceptive effects.

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