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### 四种多巴胺受体激动剂对左旋四氢巴马汀和电针镇痛的影响

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**提要** 在兔 K<sup>+</sup>透入测痛模型上, 双侧 icv 多巴胺 (DA)受体广谱激动剂 DA 和去水吗啡(Apo)以及 D<sub>1</sub>受体选择性激动剂 SKF-38393 对抗 iv 左旋四氢巴马汀 (THP) 8 mg/kg 或电针一侧“合谷”和“外关”穴引起的镇痛作用。相反, 双侧 icv D<sub>2</sub>受体选择性激动剂哌吡罗则呈剂量相关地加强 THP 或电针的镇痛作用。结果提示, THP 和电针两者的镇痛作用皆与中枢 DA 受体活动有关, 其中 D<sub>1</sub> 和 D<sub>2</sub> 受体的作用可能不同。

**关键词** 左旋四氢巴马汀; 小檗碱类; 多巴胺受体; 多巴胺; 去水吗啡; SKF-38393; 哌吡罗; 针刺; 镇痛

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## Simultaneous electric activities of pain-excitation and pain-inhibition neurons in nucleus parafascicularis of thalamus in rats during acute morphine tolerance

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**ABSTRACT** When acute morphine-tolerated rat was administered by ip morphine (10 mg/kg) which was effective before the acute tolerance to morphine, both the inhibitory effect of morphine on the electric discharges of pain-excitation neurons (PEN) in nucle-

us parafascicularis (PF) and the excitatory effect of morphine on the electric activities of pain-inhibition neurons (PIN) were simultaneously weakened, or even vanished. If a large dose of morphine (20 mg) was given ip, the modulating action of morphine on simultaneous electric discharges of PEN and PIN reappeared. It is obvious that the phenomenon of acute morphine tolerance and the antagonism to morphine tolerance can be explicitly expressed on the level of central neurons.

**KEY WORDS** morphine; drug tolerance; thalamus; electrophysiology; microelectrodes

Repeated administrations of morphine in short-term caused a gradual diminution of the analgesic effect or even total disappearance, showing the development of acute morphine tolerance in the rat<sup>(1,2)</sup>. In these reports, the changes in the behaviors of the animals were taken as the indices to study acute morphine tolerance. We found that ip morphine (10 mg/kg) in rat not only inhibited the electric activities of pain-excitation neurons (PEN) in nucleus parafascicularis (PF), but also simultaneously excited the electric activities of pain-inhibition neurons (PIN), exhibiting the analgesic effect of morphine<sup>(3)</sup>. The purpose of this experiment was to investigate the effect of antagonism to morphine tolerance on the discharged levels of 2 kinds of pain-related neurons in PF.

## MATERIALS AND METHODS

In this experiment, the method of the electric discharges of pain-related neurons in PF on both sides was simultaneously recorded by two grass microelectrodes to study the relationships between the analgesic effect of morphine and morphine tolerance on the level of central neurons.

Forty-eight Wistar rats, ♂, weighing  $226 \pm \text{SD } 21$  g were injected sc morphine-HCl (Shenyang 1st Pharmaceutical Factory 5 mg/kg) or the equivalent volume of saline every 2 h for 6 times. Operations were performed under general anesthesia (1% chloralose + 10% urethane ip 10 ml/kg) and

local anesthesia (1% xylocaine). The head was fixed in a SN-2 stereotaxic instrument. Glass microelectrodes filled with KCl 3 mol/L were fixed in SM-11 and SM-21 micromanipulators. The tip of the electrodes was 0.5–1.0  $\mu\text{m}$  in outside diameter. The direct current resistance of the electrodes was 10–30 m $\Omega$ . Morphine-HCl was injected ip 10 mg/kg or 20 mg/rat at a time. Each pair of pain-related neurons (PEN-PEN, PIN-PIN, PEN-PIN or PIN-PEN) were continually recorded for longer than 30 min.

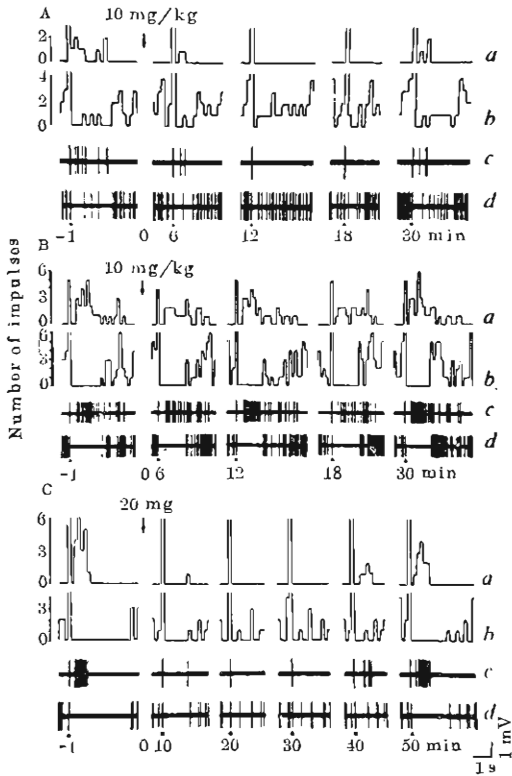
The recording, storing and processing of the experimental data, as well as the mark of the position of the microelectrode tip, all conformed to our previous report<sup>(4)</sup>.

The statistical significance of the results was determined by *t* test. All values were expressed as  $\bar{x} \pm \text{SD}$ .

## RESULTS

**Influence in rats sc with normal saline** The discharges of 11 PEN and 6 PIN were recorded in PF of 6 rats sc normal saline before the operation. Among these PEN and PIN, there were 2 pairs of the simultaneous discharges of one PEN and one PIN. The changes of the electric activities of each PEN and PIN were compared before and after ip of morphine (10 mg/kg). Fig 1 A showed that the evoked discharges of PEN in PF on one side were obviously reduced or annulled and the latency was prolonged by ip morphine, while the duration of complete inhibition of evoked discharges of PIN in PF on the other side was markedly shortened or annulled and the evoked discharges were increased, showing the coordinated activities of PEN and PIN.

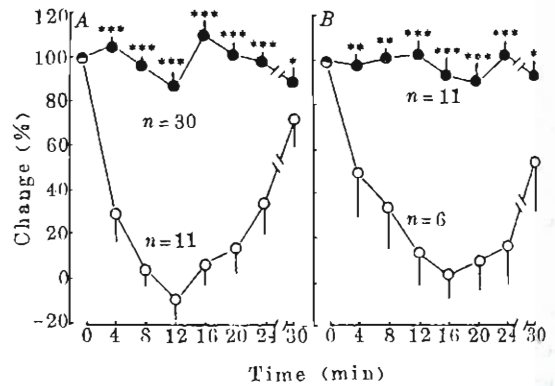
The difference of PEN or PIN between the average frequencies of evoked discharges after the nociceptive stimulation and the average frequency of the discharges within 2 s before stimulation was called the net-increased value (NIV). Before ip morphine, the NIV of the discharged frequency and the latency of 11 PEN averaged  $10 \pm 3$  Hz and  $132 \pm 46$  ms



**Fig 1.** Influence of ip morphine ( $\downarrow$ ) on the simultaneous electric activities of pain-excitation neurons (PEN) and pain-inhibition neurons (PIN) in nucleus parafascicularis of sc (A) normal saline, (B, C) morphine to rat. Histograms (upper) and the photo records (lower) of discharges in one PEN and one PIN. ( $\bullet$ ) showed the time of stimulation to sciatic nerve. (a, c) right side PEN; (b, d) left side PIN.

respectively, and the duration of the complete inhibition and the NIV of the discharged frequency of 6 PIN respectively averaged  $1.01 \pm 0.17$  s and  $-6.8 \pm 1.2$  Hz. At the 12 min after ip morphine, the average NIV of the discharged frequency of PEN was reduced to  $-0.8 \pm 0.4$  Hz, the latency was prolonged to  $444 \pm 148$  ms, the duration of the complete inhibition of PIN was shortened to  $0.15 \pm 0.08$  s, and the NIV of the discharged frequency was increased to  $1.3 \pm 0.5$  Hz. In comparison with those before ip morphine, the changes of PEN and PIN were significant ( $P < 0.01$ ).

The electric activities of PEN and PIN gradually recovered 20 min after ip morphine (Fig 2).



**Fig 2.** Effects of ip morphine 10 mg/kg ( $\downarrow$ ) on (A) frequencies of evoked discharges of PEN and (B) inhibitory durations of evoked discharges of PIN in nucleus parafascicularis of acute morphine tolerance rats ( $\bullet$ ) \* $P > 0.05$ , \*\* $P < 0.05$ , \*\*\* $P < 0.01$  vs sc normal saline (O).

**Influence in morphine-tolerated rats** The discharges of 30 PEN and 11 PIN were observed in PF of 32 rats sc morphine before the operation. Among them, 6 pairs were composed of one PEN and one PIN. The electric activities of simultaneously recorded PEN and PIN in PF on both sides did not exhibit obvious changes after ip morphine (Fig 1 B).

Before ip of morphine, the NIV of the discharged frequency and the latency of 30 PEN averaged  $8 \pm 4$  Hz and  $142 \pm 55$  ms respectively, while the average duration of the complete inhibition and the NIV of the discharged frequency of 11 PIN were respectively  $1.1 \pm 0.4$  s and  $-10 \pm 3$  Hz. At 12 min after ip morphine, the NIV of the discharged frequency, the latency of PEN, the duration of the complete inhibition and the NIV of the frequency of discharge of PIN were averaged  $7 \pm 3$  Hz,  $138 \pm 60$  ms,  $1.2 \pm 0.5$  s and  $-11 \pm 3$  Hz, respectively. These parameters of PEN and PIN did not show significant differences in comparison with those before ip of morphine, but great differences vs those sc of normal saline group ( $P < 0.01$ ). (Fig

2).

**Effects of large dose of morphine on acute morphine-tolerated rats** The discharges of 10 PEN and 7 PIN were recorded in 10 rats of acute morphine tolerance. There were 4 pairs of the simultaneous discharges of one PEN and one PIN among these PEN and PIN. After ip of morphine 20 mg, the frequency of evoked discharges of PEN in PF on one side in the acute morphine-tolerated rat not only was obviously decreased or even annulled and the latency of it was prolonged, but also the duration of the complete inhibition of PIN in PF on the other side was markedly shortened and the discharged frequency was increased (Fig 1 C).

The average NIV of the discharged frequency, 12 min after ip of morphine, of 10 PEN was reduced from  $11 \pm 4$  Hz before ip morphine to  $-1.4 \pm 0.8$  Hz, the latency was prolonged from  $170 \pm 63$  to  $445 \pm 109$  ms, while the average duration of the complete inhibition of 7 PIN was shortened from  $1.0 \pm 0.4$  to  $0.14 \pm 0.08$  s, the NIV of the discharged frequency was increased from  $-7 \pm 3$  to  $1.9 \pm 0.7$  Hz. These parameters were different from those in acute morphine-tolerated group ( $P < 0.01$ ), but were not different from those in the saline group ( $P > 0.05$ ).

## DISCUSSION

This result suggested that the analgesic effect of exogenous morphine may be produced as a consequence of coordinated functional changes of PEN and PIN in PF. Repeated administrations of morphine in short-term may have elicited a profound release of endogenous CCK-8 attenuating the analgesic effect of morphine. This may constitute an important mechanism for the development of acute morphine tolerance. It provided a valuable evidence for the hypothesis that the production and release of large amount of endogenous CCK-8 was the possible mechanism of morphine tolerance<sup>(5,6)</sup>. In addition, ip morphine 20 mg at a time could eliminate

the function of endogenous CCK-8 to PEN and PIN.

In the present work, the analgesic effect of morphine, the development of the acute tolerance to morphine and the antagonism to morphine tolerance were proved for the first time from the level of simultaneous electric activities of PEN and PIN in PF.

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急性吗啡耐受时大鼠丘脑束旁核痛兴奋和痛抑制神经元的同时电活动

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**提要** 当急性吗啡耐受大鼠 ip 耐受前有效剂量的吗啡 (10 mg/kg) 时, 吗啡对束旁核内痛兴奋神经元 (PEN) 放电的抑制作用和痛抑制神经元 (PIN) 电活动的加强作用均减弱, 甚至消失. 但 ip 大剂量吗啡 (20 mg/次) 时, 吗啡对该鼠 PEN 和 PIN 同时放电的调制作用又重新出现. 可见, 在中枢神经元水平上能明显反映出急性吗啡耐受和抗耐受现象.

**关键词** 吗啡; 药物耐受性; 丘脑; 电生理学; 微电极