Differential effects of dopamine on pain-related electric activities in normal rats and morphinistic rats

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Abstract: Objective To investigate the influence of dopamine (DA) and DA receptor's antagonist on the transmission of noxious information in the central nervous system of normal rats or morphinistic rats. **Methods** The influence of DA on the electric activity of the pain-excited neuron (PEN) in the caudate nucleus (Cd) of normal rats or morphinistic rats was recorded after the sciatic nerve was noxiously stimulated. **Results** DA shortened the average latency of the evoked discharge of PEN in the Cd of normal rats, indicating that DA could increase the activity of PEN and pain sensitivity in normal rats. This effect could be inhibited by Droperidol. DA increased the average latency of the evoked discharge of PEN in the Cd of morphinistic rats, indicating that DA could inhibit the activity of PEN and pain sensitivity in morphinistic rats. **Conclusion** The responses to painful stimulation were completely opposite between normal rats and morphinistic rats after the intracerebroventricular injection of DA.

Keywords: dopamine; morphine; pain; caudate nucleus

1 Introduction

Dopamine (DA) is the most abundant catecholaminergic neurotransmitter in the brain. It exerts many functions in the central nervous system (CNS), including regulation of pain and drugs dependence.

The abuse potential and analgesic efficacy of drugs are related. They are mediated by similar receptors, similar sites of action, and overlapping neural substrates. The mesolimbic DA pathway linking the ventral tegmentum and the ventral striatum is one of the pathways to regulate both the analgesia and reward^[1]. Opioids stimulate dopaminergic neurons in the ventral tegmental area and increase DA release in the nucleus accumbens, which leads to a reward response^[2]. The antagonist of DA can block the DA receptor, and attenuate the reward effect of opioids^[3]. Previous pharmacological studies have indicated that functional interactions may exist between the opioidergic and dopaminergic neurons.

This research was to observe the influence of DA and its antagonist droperidol on the electrical activities of pain-excited neurons (PENs) in the caudate nucleus (Cd), in order to investigate the impact of DA and its antagonist on the pain sensation in normal and morphinistic rats.

2 Materials and methods

2.1 Instruments Cerebral solid orientation apparatus (SN-2, Narishige), microelectrode operator SM-1 and SM-12 (Nashige), amplifier (JSD-731-F, Radion Factory of Guangdong Normal College), Oscillometer (VC-9, Nihon Kohden), bi-track tape recorder (ST-CH707X, Panasonic), automatic injector (ZCZ-50, Medical Instrument Experiment Factory of Zhejiang Medical University), data analyzer (PowerLab/8s, ADInstruments Pty Ltd), and electronic stimulator (SEN-3301, Nihon Kohden).

2.2 Animal grouping One hundred and twenty Wistar rats (male or female, 230-260 g), including sixty normal rats and sixty morphinistic rats, were obtained from the Center of Experimental Animals of the Second Affiliated Hospital of Harbin Medical University. The sixty normal animals and sixty morphinistic rats (morphine hydrochloride was injected subcutaneously)^[4] were separately divided into four groups (Tab. 1): saline group (control, $n = 10$), 10 μ L saline was injected; DA group ($n = 20$), 50 μ g/ 10 μ L of DA was

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Tab. 1 Animal grouping

	saline (Control)	DA (50 µg/ 10 µL)	DA (50 µg/ 10 µL) + droperidol (1 µg/ 8 µL)	droperidol (1 µg/ 8 µL)
Normal rats	Group A	Group B	Group C	Group D
morphinistic rats	Group A'	Group B'	Group C'	Group D'

injected; DA + droperidol group ($n = 20$), 1 µg/ 8 µL of droperidol was injected 2 min after DA application; and droperidol group ($n = 10$), 1 µg/ 8 µL of droperidol was injected. All chemicals were i.c.v. injected evenly by the automatic injector within 2 min.

2.3 Methods Rats were anesthetized by injection of a mixture of 500 mg/kg of ethyl carbamate and 50 mg/kg of chloridized curarine into the abdominal cavities. Routine surgery was operated after rats lost consciousness, with artificial respiration at 60 times/min. Chemicals were administered as described above in 2.2 section. Then the rat head was fixed on a cerebral solid orientation apparatus and orientated according to the B coordinate system of Pellegrino atlas [Cd (A: 2.0-2.8 mm; L: 1.5-3.5 mm; H: 3.5-5.5 mm)]. A stainless tube with an external diameter of 0.8 mm was inserted into the lateral ventricle (A: 0.1; R: 1.5; H: 3.0) for injection^[5]. The glass microelectrode with 3 mol/L of KCl solution inside (direct current resistance, 10-30 MΩ) was fixed on another operator SM-21 and inserted into the left Cd of rat to induce electric discharges. The signal of electric discharge was displayed on the oscilloscope through an amplifier and recorded by a bi-track tape recorder. Data were processed by the data analyzer and analyzed by Chart 5.3 software. The stimuli on the sciatic nerve by series impulse (voltage strength 28 V, wave width 0.3 ms, with an interval of 5 ms; 5 pulses included in one series impulse) were acted as the noxious stimulation, and articular movement and hair touching were set as the non-noxious stimulation to identify the pain reactive neuron.

2.4 Statistical analysis Data were expressed as mean $\pm$ SD. SPSS 13.0 was introduced in statistical analysis. $P < 0.05$ was considered statistically significant.

3 Results

3.1 Effect of DA on the electrical activities of PENs in the Cd of normal rats In the normal rats, the average latency of the evoked discharge of PENs in group B shortened significantly compared with the control (Saline, group A).

The average latency was (205.26 $\pm$ 13.65) ms before DA injection. It decreased to (151.11 $\pm$ 11.53) ms at 2 min after DA injection, and further shortened to (91.17 $\pm$ 9.81) ms at 10 min. The average latencies between group B and group A during 6-16 min after DA injection were significantly different ($P < 0.05$ or $P < 0.01$). The latency started to recover at 22 min after the DA injection.

The electric activity of PEN increased after DA injection, and this effect could be antagonized by droperidol. The average latency was (203.71 $\pm$ 11.87) ms before DA injection. At 2 min after injection of DA, it decreased to (181.63 $\pm$ 10.24) ms. This enhancement of PEN electric activity started to reduce at 2 min after the droperidol injection, and prolonged to (277.83 $\pm$ 18.53) ms at 10 min. Differences between group C and group A during 2-14 min after the droperidol injection were significant ($P < 0.05$ or $P < 0.01$). The latency started to recover at 18 min after the droperidol injection. There was no significant difference between group C and group D. (Fig. 1)

3.2 Effect of DA on the electrical activities of PENs in the Cd of morphinistic rats In the morphinistic rats, the average latency of the evoked discharge of PEN in group B' was obviously enhanced after the i.c.v. injection of DA compared with the control (group A'). Before DA injection, the average latency was (89.59 $\pm$ 7.65) ms. The average latency was (106.43 $\pm$ 12.39) ms at 2 min after DA injection, and further increased to (152.47 $\pm$ 8.15) ms at 8 min. Differences between group B' and group A' during 6-16 min after the DA injection were significant ($P < 0.05$ or $P < 0.01$). The latency started to recover at 18 min after the DA injection.

In the morphinistic rats, the electric activities of PENs decreased after DA injection, while the i.c.v. injection of droperidol could block this effect. Before the injection of DA, the average latency was (88.32 $\pm$ 7.54) ms, and it prolonged to (105.76 $\pm$ 11.29) ms at 2 min after DA injection. This decreased PEN electric activity started to augment at 2 min after the injection of droperidol. The latency reduced to (53.42 $\pm$ 5.09) ms at 10 min after the droperidol injection.

Differences between group C' and the group A' during 4–14 min after droperidol injection were significant ($P < 0.05$ or $P < 0.01$). The latency started to recover at 20 min after the droperidol injection. There was no significant difference between group C' and group D' in morphinistic rats. (Fig. 2)

Fig. 1 Effects of i.c.v. injection of DA and droperidol on the average latency of PENs in the Cd of normal rats. N: injection of DA for group C; 0: injection of droperidol for groups C and D, or injection of saline and DA for groups A and B, respectively. * $P < 0.05$, ** $P < 0.01$ vs group A.

Fig. 2 Effects of i.c.v. injection of DA and droperidol on the average latency of PENs in the Cd of morphinistic rats. N: injection of DA for group C'; 0: injection of droperidol for groups C' and D', or injection of saline and DA for groups A' and B', respectively. * $P < 0.05$, ** $P < 0.01$ vs group A'.

4 Discussion

Our results showed that the average latency of the evoked discharge of PENs decreased in the normal rats

while increased in the morphinistic rats after DA was injected in the Cd, indicating that DA could enhance the PEN activity and pain sensitivity in normal rats but lower them in morphinistic rats. Droperidol could inhibit the effects of DA. These demonstrated that the response to pain stimulation was quite different between normal rats and morphinistic rats after i.c.v. injection of DA.

The pain experience includes a sensory-discriminative and an emotional-affective component. The study of the sensory dimension of pain at genic, molecular, cellular, and systemic levels has progressed greatly during the past four decades^[6]. Evidences indicate that the striatum (the putamen and Cd) and striatal DA receptors are involved in regulating pain sensation in experimental and clinical conditions^[7]. Cd receives the sensory information including the sense of pain from all sensory systems, and the excitation of caudate-putamen nucleus could induce analgesia^[8]. The present results demonstrated that DA in the Cd had positive effect on pain in normal rats, verifying that DA neurons play an important role in mediating pain sensation.

On the contrary, the response to painful stimulation in morphinistic rats was quite different from that in normal rats after DA administration, since DA had inhibitory effects on the painful stimulation in morphinistic rats. The affective state induced by drugs of abuse produces an indifference to pain (or affective analgesia), a state in which nociceptive input cannot to arouse the distressing or aversive motivational state that it normally could, which may be due to the adaptive changes of neurons to morphine. One important change is the up-regulation or down-regulation of DA receptors. It is reported that there were some alterations in DA receptors induced by morphine in the caudate putamen and the ventral midbrain^[9].

Droperidol is a DA D₂ receptor antagonist that produces marked tranquilization and sedation^[10]. The present studies showed that droperidol inhibited DA's analgesic effect in morphine dependence rats. The analgesic effect maybe related to the expression changes of DA receptor subtypes in morphinistic rats. Changes of D₂ receptor during morphine dependence maybe play a role. Both DA D₁ and D₂ receptors exist in the Cd^[3]. These results suggest the different roles of DA receptors in anti-nociception and the possibility of the interaction between the DAergic and opioid systems. As reported previously by Ben-Sreti *et al.*, the D₁ agonist SKF 38393 failed to alter the nociceptive responsiveness, while the D₂ agonists LY141865 produced

an anti-nociceptive effect^[11]. Different effects of DA between normal and morphine dependence rats also maybe due to the long-lasting hyporeactivity of Cd dopaminergic nerve terminals in rats. Further study on these area will deepen our knowledge about the analgesic effect and dependence of drugs.

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References:

- [1] Franklin KBJ. Analgesia and abuse potential: an accidental association or a common substrate? *Pharmacol Biochem Behav* 1998, 59: 993-1002.
- [2] Hemby SE. Morphine-induced alterations in gene expression of calbindin immunopositive neurons in nucleus accumbens shell and core. *Neuroscience* 2004, 126: 689-703.
- [3] Li F, Shu SY, Bao XM. Structure and function of dopamine receptors. *Chin J Neurosci* 2003, 19: 405-410. (Chinese, English abstract)
- [4] Zhao CY, Yan LX, Lu N, Zhang JY, Xu MY. Making the model quickly for morphinomania in rats. *J Harbin Med Univ* 2001, 35: 257-258. (Chinese, English abstract)
- [5] Pellegrino LJ, Pellegrino AS, Cushman AJ. A stereotaxic atlas of rat brain. 2nd edition. New York: Plenum Press, 1979, 18-22.
- [6] Zhang YQ, Zhao ZQ, Ji RR. Emotional distress and related memory of pain: a neurobiological review. *Neurosci Bull* 2005, 21: 10-17.
- [7] Hagelberg N, Jaaskelainen SK, Martikainen IK, Mansikka H, Forssell H, Scheinin H, *et al.* Striatal dopamine D2 receptors in modulation of pain in humans: a review. *Eur J Pharmacol* 2004, 500: 187-192.
- [8] Wu GJ, Chen ZQ, Shi H. Roles of globus pallidus in acupuncture analgesia and exciting caudate-putamen nucleus-induced analgesia. *Chin J Neurosci* 2002, 18: 621-625. (Chinese, English abstract)
- [9] Spangler R, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF. Elevated D3 dopamine receptor mRNA in dopaminergic and dopaminergic regions of the rat brain in response to morphine. *Brain Res Mol Brain Res* 2003, 111: 74-83.
- [10] Cure S, Rathbone J, Carpenter S. Droperidol for acute psychosis. *Cochrane Database Syst Rev* 2004, 4: CD002830.
- [11] Ben-Sreti MM, Gonzalez JP, Sewell RD. Differential effects of SKF 38393 and LY 141865 on nociception and morphine analgesia. *Life Sci* 1983, 33 Suppl 1: 665-668.

多巴胺对正常和吗啡成瘾大鼠疼痛相关电活动的不同作用

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摘要: **目的** 研究多巴胺对正常大鼠和吗啡成瘾大鼠中枢的伤害性刺激的传递的影响。**方法** 在给予坐骨神经伤害性刺激后, 记录中枢痛兴奋神经元的电活动, 观察多巴胺对正常大鼠和吗啡成瘾大鼠中枢痛兴奋神经元电活动的影响。**结果** 正常大鼠中, 多巴胺使尾核痛兴奋神经元的痛诱发放电潜伏期缩短, 说明多巴胺可使正常大鼠尾核痛兴奋神经元的活动增强, 多巴胺受体拮抗剂氟哌利多可以阻断这种作用。吗啡大鼠中, 多巴胺使尾核痛兴奋神经元的痛诱发放电潜伏期延长, 说明多巴胺可使吗啡大鼠尾核痛兴奋神经元的活动减弱。**结论** 脑室注射多巴胺后, 正常大鼠和吗啡成瘾大鼠的尾核对痛刺激的反应存在着差异。

关键词: 多巴胺; 吗啡; 痛觉; 尾核