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Relationship between electroacupuncture analgesia and dopamine receptors in nucleus accumbens[1]

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KEY WORDS electroacupuncture analgesia; neucleus accumbens; SK&F-38393; quinpirole; *l*-tetrahydropalmatine; dopamine D_1 receptors; dopamine D_2 receptors

AIM: To study the roles of dopamine (DA) D_1 and D_2 receptors in nucleus accumbens in electroacupuncture analgesia (EAA) and the potentiation of EAA of rats induced by *l*-tetrahydropalmatine (*l*-THP), a dopamine receptor antagonist. **METHODS**: SK&F-38393 and quinpirole hydrochloride (Qui), highly selective agonists of D_1 and D_2 receptors, respectively were injected into nucleus accumbens of rats. **RESULTS**: SK&F-38393 (5 and 10 μg) attenuated the potentiation of EAA induced by *l*-THP, 10 μg SKF38393 attenuated EAA as well, while Qui (10 and 20 μg) had no effect on EAA and the potentiation of EAA induced by *l*-THP. **CONCLUSION**: D_1 but not D_2 receptor in nucleus accumbens play an important role in EAA and the potentiation of EAA induced by *l*-THP.

Dopamine (DA) receptor antagonists potentiate electroacupuncture analgesia (EAA)[1-3] and agonists attenuate EAA[4,5]. As a DA receptor antagonist[6], *l*-THP potentiates EAA in rabbits and human[1,7]. However the subtle mechanism underlying the roles of DA receptor subtypes in EAA is still unknown. The present study was to observe the effect of D_1 and D_2 receptor activation in nucleus accumbens on EAA and the potentiation of EAA by *l*-THP, to further explore the relationship between EAA and DA receptors in central nervous system.

MATERIALS AND METHODS

Rats Sprague-Dawley rats of either sex ($n = 107$, 220 ± s 20 g) bred by Shanghai Laboratory Animal Center, (Chinese Academy of Sciences, China) were divided into 14 groups: (1) EA + NS, (2) EA + SKF 5 μg, (3) EA + SKF 10 μg, (4) EA + Qui 10 μg, (5) EA + Qui 20 μg, (6) SKF 5 μg (7) SKF 10 μg (8) Qui 10 μg, (9) Qui 20 μg, (10) EA + *l*-THP + NS, (11) EA + *l*-THP + SKF 5 μg, (12) EA + *l*-THP + SKF 10 μg, (13) EA + *l*-THP + Qui 10 μg, (14) EA + *l*-THP + Qui 20 μg.

Drugs and microinjections *L*-tetrahydropalmatine sulfate injection (*l*-THP, Zhanjiang Pharmaceutical Co) was injected iv at a dose of 1.5 mg·kg^{-1}. (+)-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol (SK&F-38393, SKF) and quinpirole hydrochloride (Qui) were injected into nucleus accumbens via the stainless steel cannula (0.8 mm OD, 0.5 mm ID) implanted into nucleus accumbens according to Konig & Klippel atlas (A9.4 mm, R1.3 mm, H6.3 mm). SK&F-38393 and Qui were dissolved in 0.9 % saline. Microinjection volume was 1 μL in 5 min. At the end of each experiment, the position of the cannula was verified histologically.

Nociceptive test[8] Rat tail was inserted subcutaneously with needles which were connected with pain test apparatus (Model WQ-9E Pain Threshold Meter, Beijing). The least intensity of stimulating current that induced the tail flick was recorded as pain threshold. The pain threshold test was repeated thrice as the preadministration control, which ranged from 0.1 to 0.2 mA in normal rats.

Electroacupuncture (EA) Unilateral "Zu-San-Li" (St 36, between the muscle anterior tibialis and muscle extensor digitorum longus) and "Kun-Lun" (UB60, between the tip of the external malleolus and tendo calcaneus) points of each rat were needled and stimulated with an electrical stimulator (Model G6805-2, Shanghai). Dense-sparse frequency of wave was selected and the intensity was adjusted to the extent which provoked light tremble of limb. EA lasted 40 min.

Statistical analysis The $\bar{x} \pm s$ of the groups were compared with t-test.

RESULTS

No significant changes of pain threshold were found after microinjection of SK&F-38393 or Qui into nucleus accumbens (Tab 1). EA elevated pain threshold remarkblely. The microinjection of 5 μg SK&F-38393 5 min after the beginning of EA had no significant effect on EA, while 10 μg antagonized EAA 20 - 80 min after the beginning of EA. Qui (10 and

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Tab 1. Effects of SK&F-38393 (SKF) or quinpirole (Qui) injected into nucleus accumbens on the pain threshold of rats. $n = 6$, $\bar{x} \pm s$. $^aP > 0.05$ *vs* control.

Compound	Pain threshold after injection/mA								
	Control	10 min	20 min	30 min	40 min	50 min	60 min	80 min	100 min
SKF (5 μg)	0.12 ± 0.04	0.13 ± 0.04[a]	0.12 ± 0.03[a]	0.10 ± 0.02[a]	0.11 ± 0.04[a]	0.12 ± 0.04[a]	0.13 ± 0.04[a]	0.12 ± 0.02[a]	0.12 ± 0.04[a]
SKF (10 μg)	0.13 ± 0.04	0.13 ± 0.06[a]	0.15 ± 0.09[a]	0.13 ± 0.05[a]	0.12 ± 0.03[a]	0.13 ± 0.05[a]	0.12 ± 0.03[a]	0.11 ± 0.02[a]	0.13 ± 0.03[a]
Qui (10 μg)	0.12 ± 0.03	0.11 ± 0.03[a]	0.14 ± 0.02[a]	0.13 ± 0.07[a]	0.14 ± 0.07[a]	0.13 ± 0.04[a]	0.13 ± 0.02[a]	0.13 ± 0.04[a]	0.12 ± 0.02[a]
Qui (20 μg)	0.13 ± 0.06	0.14 ± 0.04[a]	0.15 ± 0.04[a]	0.16 ± 0.03[a]	0.17 ± 0.05[a]	0.15 ± 0.03[a]	0.14 ± 0.02[a]	0.15 ± 0.04[a]	0.15 ± 0.04[a]

20 μg) injected into nucleus accumbens had no significent effect on EAA (Tab 2).

L-THP 15 mg · kg^{-1} (ip) 10 min after the beginning of EAA potentiated EAA markedly. SK&F-38393 5 and 10 μg injected into nucleus accumbens attenuated the potentiation of EAA induced by *l*-THP. *In contrast, Qui (10 and 20 μg) had no significant* effect on the potentiation of EAA induced by *l*-THP (Tab 3).

DISCUSSION

Increasing attention had been paid on the role of nucleus accumbens in pain modulation which is known to be rich in DA receptors[9,10]. In our study, injection of D_1 receptor agonist SK&F-38393 into nucleus accumbens attenuated EAA (Tab 2) and the potentiation of EAA induced by *l*-THP (Tab 3), which is consistant to the results of icv[11,12]. Qui was

Tab 2. Effects of SK&F-38393 (SKF) or quinpirole (Qui) injected into nucleus accumbens of rats on electroacupuncture analgesia (EA). SKF and Qui were injected at 5 min after the start of electroacupuncture. Electroacupuncture continued for 40 min. $n = 6$ except for EA + NS $n = 9$. $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* corresponding EA + NS.

EA +	Base line pain threshold/mA	Changes of pain threshold after the start of EA/mA							
		10 min	20 min	30 min	40 min	50 min	60 min	80 min	100 min
NS	0.11 ± 0.06	0.11 ± 0.05	0.14 ± 0.05	0.14 ± 0.04	0.11 ± 0.05	0.12 ± 0.05	0.11 ± 0.05	0.09 ± 0.05	0.07 ± 0.07
SKF (5 μg)	0.10 ± 0.05[a]	0.08 ± 0.04[a]	0.12 ± 0.04[a]	0.13 ± 0.03[a]	0.11 ± 0.05[a]	0.10 ± 0.07[a]	0.08 ± 0.06[a]	0.08 ± 0.06[a]	0.06 ± 0.04[a]
SKF (10 μg)	0.12 ± 0.05[a]	0.06 ± 0.03[a]	0.07 ± 0.05[b]	0.07 ± 0.04[c]	0.07 ± 0.05[a]	0.05 ± 0.06[b]	0.02 ± 0.08[b]	0.01 ± 0.08[b]	0.01 ± 0.06[a]
Qui (10 μg)	0.11 ± 0.03[a]	0.08 ± 0.02[a]	0.09 ± 0.02[a]	0.13 ± 0.04[a]	0.14 ± 0.01[a]	0.12 ± 0.03[a]	0.10 ± 0.01[a]	0.08 ± 0.02[a]	0.05 ± 0.01[a]
Qui (20 μg)	0.11 ± 0.05[a]	0.08 ± 0.02[a]	0.11 ± 0.04[a]	0.13 ± 0.03[a]	0.11 ± 0.03[a]	0.09 ± 0.02[a]	0.08 ± 0.02[a]	0.07 ± 0.04[a]	0.04 ± 0.04[a]

Tab 3. Effects of SK&F-38393 (SKF) or quinpirole (Qui) injected into nucleus accumbens of rats on the potentiation of electroacupuncture analgesia (EA) induced by *l*-tetrahydropalmatine. SKF and Qui were injected at 5 min after the start of electroacupuncture analgesia. *L*-THP were administered at 10 min after the start of electroacupuncture. $n = 6$ except for EA + *l*-THP + NS $n = 8$, EA + *l*-THP + Qui 20 μg $n = 7$, $\bar{x} \pm s$. $^bP > 0.05$, $^cP < 0.01$ *vs* corresponding EA + *l*-THP + NS.

EA + *l*-THP +	Base line pain threshold/mA	Changes of pain threshold after the start of EA/mA							
		10 min	20 min	30 min	40 min	50 min	60 min	80 min	100 min
NS	0.09 ± 0.06	0.10 ± 0.05	0.24 ± 0.11	0.290 ± 0.07	0.28 ± 0.07	0.31 ± 0.08	0.30 ± 0.06	0.24 ± 0.10	0.21 ± 0.05
SKF (5 μg)	0.09 ± 0.03[a]	0.10 ± 0.02[a]	0.19 ± 0.03[a]	0.24 ± 0.04[a]	0.23 ± 0.04[a]	0.21 ± 0.03[b]	0.21 ± 0.03[c]	0.16 ± 0.03[b]	0.15 ± 0.03[a]
SKF (10 μg)	0.12 ± 0.05[a]	0.10 ± 0.03[a]	0.16 ± 0.05[a]	0.15 ± 0 03[c]	0.17 ± 0.07[b]	0.16 ± 0.05[c]	0.16 ± 0.03[c]	0.14 ± 0.05[c]	0.09 ± 0.04[c]
Qui (10 μg)	0.12 ± 0.03[a]	0.10 ± 0.02[a]	0.17 ± 0.02[a]	0.25 ± 0.06[a]	0.34 ± 0.03[a]	0.27 ± 0.08[a]	0.26 ± 0.06[a]	0.23 ± 0 06[a]	0.16 ± 0.02[a]
Qui (20 μg)	0.09 ± 0.04[a]	0.11 ± 0.03[a]	0.31 ± 0.07[a]	0.38 ± 0.09[a]	0.31 ± 0.04[a]	0.36 ± 0.06[a]	0.32 ± 0.02[a]	0.28 ± 0.05[a]	0.18 ± 0.06[a]

formerly reported to potentiate EAA when administered icv, while the injection of it into nucleus accumbens had no marked effect in our study (Tab 2, 3) which suggest the complication of the role of D_2 receptor in EAA. However, whether D_2 receptor has a nucleus specific effect on EAA needs to be investigated in more nuclei and on more animal models of nociceptive test which are the shortcomings of our study. The present study demonstrated that the D_1 but not D_2 receptor played an important role at least in nucleus accumbens, in EAA and the potentiating effect of *l*-THP on EAA.

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大鼠伏膈核内多巴胺受体与电针镇痛的关系

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关键词 电针镇痛；伏膈核；SK&F-38393；喹吡罗；左旋四氢巴马汀；多巴胺 D_1 受体；多巴胺 D_2 受体

目的：研究多巴胺受体拮抗剂左旋四氢巴马汀（*l*-THP）加强电针镇痛（EAA）的原理，阐明中枢神经系统内多巴胺（DA）系统在 EAA 中的作用。**方法**：分别将 D_1 受体激动剂 SK&F-38393 和 D_2 受体激动剂 quinpirole hydrochloride（Qui）注射入大鼠伏膈核，观察对 EAA 及 *l*-THP 加强 EAA 的作用。**结果**：SK&F-38393（5 μg，10 μg）明显对抗了 *l*-THP 加强 EAA 的作用，10 μg SK&F-38393 则减弱 EAA；Qui（10 μg，20 μg），对 EAA 及 *l*-THP 加强 EAA 的作用没有显著影响。**结论**：伏膈核内 D_1 受体活动在 EAA 及 *l*-THP 加强 EAA 中起重要作用，D_2 受体没有显著作用。