不改变；CF 下降；MVO_2 及效率改变不明显. DLF 也能增强离体豚鼠乳头肌等长收缩张力，增加麻醉狗的 LVP 及 dP/dt_{max}，但离体右心房自发搏动频率及左心房兴奋阈不受影响. DLF 引起的心脏衰竭和它的冠脉收缩作用有关.

关键词 眼镜蛇毒；直接溶解因子；心肌收缩；心脏功能试验

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Effects of phencyclidine on contractile forces of isolated rabbit papillary muscles[1]

DAI Jia-Le, XU Shao-Fen (*Department of Neurobiology, Shanghai Medical University, Shanghai 200032, China*)

ABSTRACT Phencyclidine (PCP) (0.01–50 μmol · L^{-1}) and its analogue, TCP (0.01–50 μmol · L^{-1}) exhibited positive inotropic effects on electrically stimulated rabbit papillary muscle preparations. Dextrorphan (5 or 10 μmol · L^{-1}) antagonized the actions of PCP in non-competitive manner ($pD_2' = 5.25$). This demonstrated the involvement of PCP receptors in the positive inotropic effects of PCP. By using high performance liquid chromatography with electrochemical detector (HPLC-ECD), an increase of DOPAC content was found in bath medium after PCP addition. Each of the dopamine receptor antagonists SCH23390, haloperidol and sulpiride (1 μmol · L^{-1}) attenuated the maximal inotropic effects of PCP. These results suggest that PCP induces positive inotropic effects by increasing the release and / or blocking the uptake of dopamine.

KEY WORDS papillary muscles; phencyclidine; high pressure liquid chromatography; dextrorphan; dopamine

Phencyclidine (PCP) has well-described effects on the cardiovascular system[1,2]. There were contradictory reports of positive[3] and negative[4] inotropic effects of PCP on ventricular muscle preparations. Radioligand binding assay demonstrated the existence of specific PCP receptors in guinea pig and rat hearts[2]. Activation of PCP receptors increased the release and blocked the uptake of norepinepherine (NE)[5], dopamine (DA)[6], etc. The purpose of the present study is to investigate the involvement of PCP receptors in inotropic effects of PCP on papillary muscles, and to examine the relationship between monoamine transmitters and the inotropic actions, to explore the mechanism of effects of PCP on ventricular muscles.

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MATERIALS AND METHODS

PCP was synthesized by Shanghai Medical University. Dextrorphan, SCH23390 and *N*-(1-[2-thienyl]cyclohexyl)3,4-piperidine (TCP) were kindly donated by Prof Avram Goldstein (Addiction Research Foundation, USA), Prof Reizo Inoki (Osaka University, Japan) and Beijing Military Medical Institute, respectively. Haloperidol and sulpiride were purchased from Shanghai Tianfeng Pharmaceutical Factory.

Rabbits of either sex, weighing 2.61 ± SD 0.23 kg, were stunned by a blow to the head, and the right heart papillary muscles were dissected free, suspended vertically under 1.0 g of tension, and incubated in a bath containing 4 ml of Tyrode's solution (pH = 7.4). The soluion was gassed with 95% O_2 +

5% CO_2 gas mixture, and maintained at 30 ± 0.5℃. Papillary muscles were stimulated through a pair of bipolar platinum electrodes by electrical pulses (0.3 ms, 1.0 Hz, 1.0 V), and developed tensions were monitored with a force–displacement transducer and a pen–recorder (LM14). After 60 min equilibration, the preparation was exposed to drugs cumulatively. The interval between concentrations was 10 min.

Monoamines and their metabolites were detected by ion–pair reverse phase HPLC with electrochemical detector. HPLC–ECD system (Waters) consisted of a M510 pump, a U6K injection system coupled to a M460 electrochemical detector and a M740 data module. Determination condition was controlled as previously reported[7]. Samples of 1 ml incubation medium were collected before and 10 min after PCP administration, lyophilized and stored at −30℃. Before detection, the lyophilized samples were dissolved in purified water, and the injection volume was 50–100 μl.

Developed tension = (contractile forces after administration − contractile forces before administration). Results are presented as $\bar{x} \pm$ SD. Statistical significance was examined by paired t test.

RESULTS

Effects of PCP and TCP on contractile forces of rabbit papillary muscles PCP or TCP was cumulatively injected into the bath medium at 10 min interval. PCP (final concentration 0.01–50 μmol · L^{-1}) increased the contractile forces in a concentration dependent manner. TCP (0.01–50 μmol · L^{-1}), a selective PCP ligand, induced analogous concentration dependent effects (Fig 1). The maximal effects of PCP were more potent than those of TCP.

Effects of dextrorphan on inotropic actions of PCP Dextrorphan, an antagonist for PCP receptors[8], was added into the bath medium 10 min prior to PCP administration.

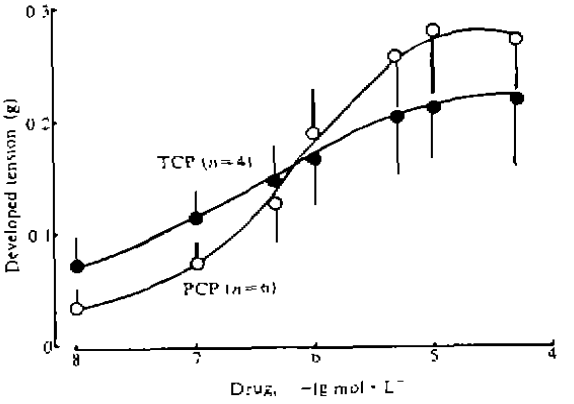

Fig 1. Effects of phencyclidine (PCP) and *N*–(1–2–thienyl cyclohexyl) 3,4–piperidine (TCP) on contractile forces of rabbit papillary muscles. $\bar{x} \pm$ SD.

Although there was little change of contractile force after dextrorphan administration, dextrorphan (5 or 10 μmol · L^{-1}) significantly inhibited the positive inotropic effects of PCP (Fig 2). As shown in log concentration–response curve, the maximal height was decreased as compared with the control. The curve did not shift parallelly to the right. This phenomena suggested that dextrorphan antagonized PCP actions in a non–competitive manner on rabbit papillary muscle preparations ($pD_2' = 5.25$).

Effect of PCP on monoamine contents NE, DA and DOPAC, but not MHPG,

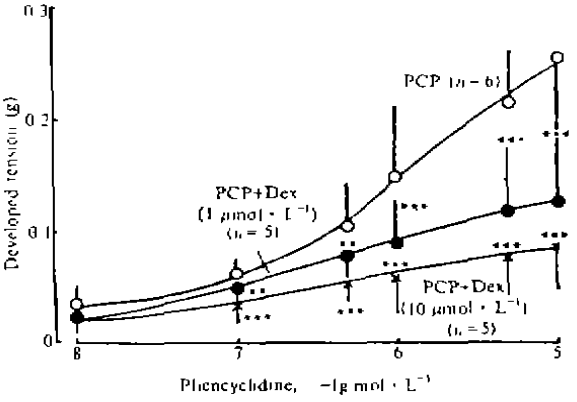

Fig 2. Effects of dextrorphan (Dex) on inotrpic actions of phencyclidine (PCP) in rabbit papillary muscles. $\bar{x} \pm$ SD. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

Tab 1. Contents of monoamines and their metabolites (ng · ml^{-1}) in incubation medium of electrically paced rabbit papillary muscles after PCP administration. $\bar{x} \pm$ SD. $^{*}P > 0.05$, $^{**}P < 0.05$. Digit in the parentheses represents the number of tested preparations.

	Normal saline		Phencyclidine (5 μmol · L^{-1})	
	before	after	before	after
NE	5 ± 4(5)	5 ± 3(5)*	6 ± 3(7)	7 ± 4(7)*
DA	0.55 ± 0.14(5)	0.50 ± 0.17(5)*	0.11 ± 0.14(6)	0.15 ± 0.29(6)*
DOPAC	0.10 ± 0.10(5)	0.09 ± 0.12(5)*	0.5 ± 0.3(6)	0.8 ± 0.4(6)**

5-HIAA and 5-HT were able to be detected in bath medium. No change in contents of monoamines and their metabolites were found before and after the administration in the normal saline control group. PCP induced little change of NE content, while DOPAC content was enhanced significantly ($P < 0.05$). DA content was not much augmented (Tab 1). Contents of DOPAC, a metabolite of DA, was high due to the fast metabolism rate. This suggested DA release from the nerve terminals be promoted and / or the uptake blocked.

Inotropic actions of PCP after DA receptor antagonists (DARA) pretreatment PCP was given to isolated rabbit papillary muscles 10 min after SCH23390, haloperidol and sulpiride (1 μmol · L^{-1}) respectively. All of the 3 DARA attenuated the inotropy induced by PCP (Fig 3). The sequence of attenuation potency was haloperidol > sulpiride > SCH23390, which showed that D_2 antagonists (haloperidol and sulpiride) were more potent than D_1 antagonists (SCH23390)[9] in inhibiting PCP actions.

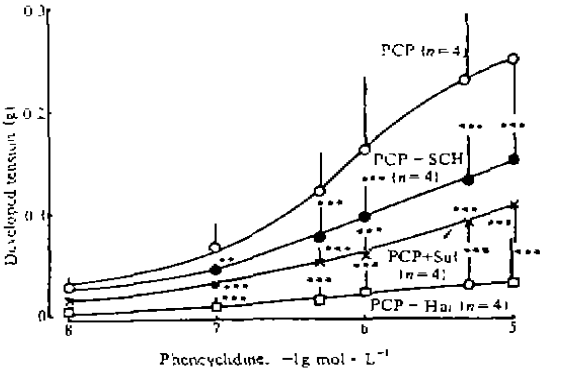

Fig 3. Effects of SCH23390 (1 μmol · L^{-1}), sulpiride (1 μmol · L^{-1}) and haloperidol (1 μmol · L^{-1}) on the inotropy induced by phencyclidine (PCP) in rabbit papillary muscles. $\bar{x} \pm$ SD. $^{*}P > 0.05$, $^{**}P < 0.05$, $^{***}P < 0.01$ *vs* control.

DISCUSSION

Radio-ligand binding assay demonstrated that PCP receptors existed in brains[10], blood vessles[1] and hearts[2]. TCP and dextrorphan were proven to be selective PCP receptor agonist and antagonist[8] respectively. Contractile forces of papillary muscles were increased by both PCP and TCP, while dextrorphan dose-dependently inhibited such actions of PCP in non-competitive manner. These results suggested the existence of PCP receptors in rabbit papillary muscles. The negative inotropy of PCP on myocardium[4] may be the result of high concentration of PCP, which was also able to be found in our data.

Many reports revealed close relationship between PCP actions and monoamines. Our results indicated an increase of DOPAC contents in bath medium after PCP administration, suggesting that PCP augmented the release and / or blocked the uptake of DA from nerve terminals, which conformed to the previous reports[6]. DA en-

hanced cardiac contractility[11], and that explained the inotropic effects of PCP. It was also proven by using DARA which inhibited PCP actions sufficiently. PCP and sigma opiate receptors were extensively overlapped in membrane preparations[1], and D_2 receptor antagonists, including haloperidol[12], inhibited the binding of sigma receptor ligands as well as PCP. This may partially explain the rank order of 3 examined DARA in inhibiting PCP actions. We had not revealed the actions of sigma receptor ligands and their interactions with DA system, and they need further investigations.

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苯环利定对离体兔乳头状肌收缩力的影响

戴佳乐、许绍芬 (上海医科大学神经生物学教研室，上海 200032，中国)

提要 苯环利定(PCP) (0.01-50 μmol · L^{-1})及 PCP 受体激动剂 TCP (0.01-50 μmol · L^{-1})在电刺激的兔乳头状肌离体标本上产生正性肌力作用，该效应呈剂量依赖关系，此效应亦被右啡烷(5 或 10 μmol · L^{-1})非竞争性拮抗(pD_2 = 5.25)，从而提示了 PCP 受体的参与. 应用高压液相-电化学检测法测定温育液中单胺类递质，发现给予 PCP 后，DOPAC 浓度上升. 多巴胺受体拮抗剂 SCH23390、氟哌啶醇、舒必利(1 μmol · L^{-1})均能抑制 PCP 的正性肌力作用，从而提示了 PCP 通过促进神经末梢多巴胺的释放和/或抑制重摄取而发挥其对兔乳头状肌的正性肌力作用.

关键词 乳头状肌; 苯环利定; 高压液相色谱法; 右啡烷; 多巴胺