鞠佃文，郑钦岳，王洪斌，方 军 （第二军医大学药学院药理教研室，上海200433，中国）

摘要 重组人 IL-1β 在1000—10 000 U·ml^{-1}，IL-6在10—1000 U·ml^{-1}，TNFα 在0.5—50 U·ml^{-1}，GM-CSF 在1—1000 ng·ml^{-1}范围内对培养的兔滑膜细胞 DNA 合成呈浓度依赖性刺激作用。来氟米特及其代谢产物 A77 1726对此有明显抑制作用。提示 IL-1，IL-6，TNF 和 GM-CSF 在关节炎的发病中有重要地位，来氟米特抑制滑膜细胞增殖可能与其特异性的抗炎作用有关。

关键词 来氟米特；A77 1726；脱氧核糖核酸；滑膜；白细胞介素-1；白细胞介素-6；肿瘤坏死因子；粒细胞-巨噬细胞集落刺激因子；细胞肽；培养的细胞

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Effects of cyproheptadine on TXB_2 and 6-keto-$PGF_{1\alpha}$ plasma levels in rabbits with hemorrhagic shock

ZHANG Qing-Zhu, WANG Qing, ZHANG Chun-Fen, LING Xiu-Zhen, LIU Wen-Yan[1], JIN Li-Ying[1] (*Department of Pharmacology, [1] Department of Physiology, Ji-ning Medical College, Ji-ning 272113, China*)

ABSTRACT Profound hemorrhagic shock was produced in 26 rabbits by exsanguination *via* carotid artery until blood pressure (BP) = 5.3 kPa (40 mmHg) for a period of 90 min. Rabbits were equally divided into a cyproheptadine (Cyp) treated group and a .control group. The blood samples before and 90 min after shock and 30 min after liquid and blood infusion and administering Cyp (10 mg·kg^{-1}) were collected from the carotid artery. With radioimmunoassay, we measured the thromboxane B_2(TXB_2) and 6-ketoprostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) contents in plasma. The results indicated that the TXB_2 and 6-keto-$PGF_{1\alpha}$ levels during shock (1024±924, 30±32) and after liquid and blood infusion (990±943, 60±54) were higher than those (221±134, 6±4) in normal rabbits ($P<0.01$, $P<0.05$). Cyp reduced obviously the TXA_2 plasma level in rabbit with shock (304±299 *vs* 990±943, $P<0.05$). We conclude that the decrease of TXB_2 content is one of the possible mechanisms of cyproheptadine anti-shock effect.

KEY WORDS cyproheptadine; hemorrhagic shock; thromboxane B_2; 6-ketoprostaglandin F1 aipha

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Our previous study showed that cyproheptadine (Cyp) had a beneficial anti-shock effect[1]. This article is to provide further experimental evidences for anti-shock effect of Cyp through the detections of thromboxane A_2 (TXA_2) and prostacyclin I_2(PGI_2) levels.

MATERIALS AND METHODS

Cyp (Changzhou 4th Pharmaceutical Factory); ^{125}I-TXB_2 and ^{125}I-6-keto-$PGF_{1\alpha}$ radioimmunoassay (RIA) kit (Research Department of Thrombus and Hemostasis, Suzhou Medical College); FMJ-182 gamma counter (Rihuan Apparatus Manufactory, Shang-

hai Institute of Atomic Energy, Chinese Academy of Sciences); Rabbits were provided by the Animal Center of this College.

The rabbit was anesthetized with 20% urethane 1 g·kg^{-1} iv and endotracheally intubated in supine position. A catheter full of 5 % sodium citrate solution was inserted into the right carotid artery and connected to a mercury manometer to measure and record the blood pressure (BP). Left jugular vein was connulated for infusion of blood, liquid, and drug. Blood samples was collected from cartoid artery. The changes of thromboxane B_2 (TXB_2) and 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) plasma contents in rabbit before and after hemorrhagic shock and after liquid and blood infusion and administering cyproheptadine (Cyp) were determined by radioimmuoassay (RIA).

Hemorrhagic shock Heparin 400 U·kg^{-1} was infused *iv*. The blood was let out to maintain the BP at 5.3 kPa (total amount of blood-letting was 25—40 ml·kg^{-1}).

Experimental protocol Rabbit of either sex weighing 2.3±*s* 0.3 kg were randomly divided into the treated (n=13) and the control (n=13) groups. Treated group: After BP being kept constant at 5.3 kPa for 90 min, a mixed liquid (equal volume of normal saline and dextran 40000) was infused 25 ml·kg^{-1} into jugular vein within 25 min. Cyp 10 mg·kg^{-1} was added to the next half of the mixed liquid. 5 min after infusion, all of the autologous blood (with sodium citrate) was reinfused. Control group received the same amount of vehicle.

Collection of blood samples 20 % edetic acid 0.3 ml was added into the plastic test tube for anticoagulation. Blood sample 3.0 ml was taken from the carotid artery of rabbits before, 90 min after shock, 30 min after transfusion, and 30 min after medication. After centrifugation, plasma 1.5 ml was stored in a small bottle with lid at −30 C.

Plasma TXB_2 and 6-keto-$PGF_{1\alpha}$ were determined by RIA[2,3].

Statistical analysis Data ($\bar{x}\pm s$) were analyzed by t test.

RESULTS

TXB_2 The plasma TXB_2 levels in rabbits during shock and after liquid and blood infusion were higher than those in normal ($P<0.01$, $P<0.05$). Compared with shock the plasma TXB_2 contents in rabbits after liquid and blood infusion were not much changed ($P>0.05$). But compared with shock and simple liquid and blood infusion (control), the concentrations of plasma TXB_2 in rabbits after Cyp (treated) were lowered markedly ($P<0.01$ and $P<0.05$, respectively) (Tab 1).

6-Keto-$PGF_{1\alpha}$ The contents after shock and liquid and blood infusion were higher than those before shock ($P<0.05$). Compared with shock, the levels after liquid and blood infusion did not show noticeable difference ($P>0.05$). Compared with control, the concentrations after Cyp were not much increased ($P>0.05$) (Tab 1).

TXB_2/6-keto-$PGF_{1\alpha}$ The ratio after shock were obviously lower than that before shock ($P<0.05$). Compared with shock, the ratios of control and treated groups were not

Tab 1. Plasma TXB_2, 6-keto-$PGF_{1\alpha}$ levels (pg·ml^{-1}) and TXB_2/6-keto-$PGF_{1\alpha}$ ratio of rabbits before and after shock and after transfusion (conirol group) and administering cyprobeptadine (treated group, 10 mg·kg^{-1}). n=13, $\bar{x}\pm s$. $^bP<0.05$, $^cP<0.01$ *vs* normal. $^dP>0.05$ *vs* shock. $^fP>0.05$, $^bP<0.05$ *vs* control.

	Before shock	After shock	After transfusion (control)	After Cyp (treated)
TXB_2	221±134	1 042±924^c	990±943^d	304±299^b
6-keto-$PGF_{1\alpha}$	6±4	30±32^b	60±54^d	74±89^f
TXB_2/6-keto*	57±45	23±17^b	30±43^d	20±28^e

* Individual comparison.

much different ($P > 0.05$). Compared with control, the difference of the ratios after Cyp was not significant ($P > 0.05$) (Tab 1).

DISCUSSION

TXA_2 is an important shockgenic factor. On the contrary, PGI_2 is a "protective hormone" of vasculature. TXA_2 and PGI_2 are rapidly metabolized into inactive TXB_2 and 6-keto-$PGF_{1\alpha}$ *in vivo*. The determination of TXB_2 and 6-keto-$PGF_{1\alpha}$ contents could directly reflect the changes of TXA_2 and PGI_2 levels[4]. Cyp is a 5-HT S_2 and histamine H_1 receptor antagonist, and a non-selective Ca^{2+} entry blocker[5,6]. It can block S_2 receptor and calcium entrance of the platelet, reduce the release of TXA_2, inhibit the platelet aggregation, and cause the decline of the TXB_2 concentration. Furthermore, Cyp was found to have scavenging effects on oxygen free radicals[7]. It has been reported that Cyp prevents the pulmonary platelet trapping (PTT) in traumatized dogs[8], and is effective in endotoxin-induced adult respiratory distress syndrome (ARDS)[9]. Our results showed that Cyp could significantly reduce the TXB_2 plasma level in rabbits with shock. But it was not parallel to the rise of 6-keto-$PGF_{1\alpha}$ ($P > 0.05$), suggesting that Cyp only affects the content of TXB_2. The decline of TXB_2 content is one of the mechanisms of Cyp anti-shock effect.

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噻庚啶对出血性休克兔血浆血栓素 B_2 和 6-酮前列腺素 $F_{1\alpha}$ 的影响

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张庆柱，王 清，张春芬，凌秀珍，刘文彦[1]，金丽英[1]（山东济宁医学院药理教研室，[1]生理教研室，济宁 272113，中国）

摘要 26只兔被随机分为治疗组和对照组：颈动脉放血至血压5.3 kPa，维持90 min，复制出血性休克模型。于休克前后，输液输血（对照组）和给药（治疗组，噻庚啶10 mg·kg^{-1}）后30 min分别由颈动脉采取血样，结果显示用药组血栓素 B_2 显著下降（$P < 0.05$），6-酮前列腺素 $F_{1\alpha}$ 升高不明显（$P > 0.05$）。噻庚啶致血浆血栓素 B_2 水平下降是其抗休克作用机制之一。

关键词 噻庚啶；出血性休克；血栓素 B_2；6-酮前列腺素 $F_{1\alpha}$