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Effect of emodin and sandostatin on metabolism of eicosanoids in acute necrotizing pancreatitis

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INTRODUCTION

In order to study the therapeutic mechanisms of emodin, an extract of Rhubarb (Rhizoma et Radix Rhei, a traditional Chinese herbal medicine), and sandostatin in the treatment of acute necrotizing pancreatitis (ANP), we used the two drugs in rat models of the disease and observed the changes of plasma thromboxane -2 (TXB_2), 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$ and prostaglandin E_2 (PEG_2).

MATERIAL AND METHODS

Animals and reagents

One hundred and sixty male Sprague-Dawley (SD) rats (Shanghai Birth Control Institute, Shanghai) weighing 220g-280g were used. Emodin (Natural Medicine Institute, Pharmacology School of Shanghai Medical University, Sh anghai); sandostatin (Sandoz Co.); sodium taurocholate (Sigma); radioimmunoassay kits of PGE_2, 6-keto-$PGF_{1\alpha}$ and TXB_2 (Institute of Thrombosis and Coagulation, Suzhou Medical College).

Methods

The rats were divided randomly into 4 groups. After fasted (water allowed over 12 hours, the rats were anesthetized with 2.5% pentobarbital (0.1 mL/100g, i.p.), and a constant venous infusion route (1 mL/h) was established via *vena femoralis*. The peritonaeum cavity was then cut open and the pancreatocholangioduct was cramped at both the duodenal and hepatoportal ends before 5% sodium taurocholate solution (0.1 mL/100 g) was injected into the duct for 1 minute followed by a pause of 4 minutes. Then, the following drugs were infused intravenously: emodin, 0.25 mg/100 g, every 6 hours in emodin group; or sandostantin, 0.2 μg/100 g in sandostatin group, or normal saline in sham-operation group in which no taurocholate was used or in controls. The rats were killed 3, 6 and 12 hours after onset of the disease and the survival number was recorded. Samples of blood, ascites and pancreas were collected for detection of PGE_2, TXB_2, 6-keto-$PGF_{1\alpha}$ (RIA), serum amylase, lipase (Bech man Biochem System and Kits) and pathological observation under light microscope or transmission electronmicroscope (TEM). Pancreatic pathological scoring was made by Schmidt method[1] double-blindedly.

Statistics

Test of homogeneicy of variance, analysis of variance, Student-Newman-Keauls (SNK) test, *t* or *t'* test and χ^2 test.

RESULTS

Survival rate of the rats

The 12 hour survival rate in emodin group was 56.3% (9/16) and 62.5% (10/16) in sandostatin group; both were signifincantly higher than that of con trol group (23.8%, 5/21; $P<0.05$, $P<0.01$). However, no significant difference was found between emodin and sandostatin groups.

Metabolites of eicosanoids

TXB_2 detected at 3, 6, and 12 hours after ANP in control group was significantly higher than that of sham-operation group, the highest value, 4.5 times was at 6 hours ($P<0.01$, Table 1), while 6-keto-$PGF_{1\alpha}$ in each detection was lower as compared with that of sham. operation group, but no significant difference was found. TXB_2 was decreased obviously in each detection in both emodin, and sandostatin groups in comparison with that of control group ($P<0.01$). But at 12 hours after ANP, TXB_2 was lower in emodin group than that of sandostatin group. PGE_2 or 6-keto-$PGF_{1\alpha}$ was higher in the 2 drug-given groups than that of control group, but with no statistical significance.

Enzyme activities, ascites volume and pathological findings

Serum amylase, lipase and ascites were significantly

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lower in two drug-given groups than that in control group ($P<0.05$). In sandostatin group, two enzyme parameters were lower than that in emodin group, but only amylase showed significant difference ($P<0.01$). Compared with that in control group, the pathalogical scores of necrosis of acinar cells were markedly lower either in emodin or sandostatin group ($P<0.05$; $P<0.01$, Table 2), but there was no significant difference between the 2 drug-given groups. Obvious karyopyknosis, nuclear degeneration, cytoclasis, and lots of microthrombi in capillaries were found under TEM in control group, while in 2 drug-given groups, there were much less acinar necrosis and microthrombosis, and the major changes were pachynesis, autophagocytic vacuoles or bodies, swollen mitochondria and distorted endoplasmic reticulum.

Table 1 Results of detection of metabolites of eicosanoids in 4 groups of rats with ANP (ng/L, $\bar{x}\pm s$)

Groups	TXB_2			6-keto-$PGF_{1\alpha}$		
	3 h	6 h	12 h	3 h	6 h	12 h
Emodin	290.16±145.62(6)[ad]	335.63±191.69(5)[b]	67.71±38.54(6)[b]	111.70±16.76(6)	127.68±12.35(6)[bc]	79.09±30.17(6)
Sandostatin	82.40±21.59(7)[b]	193.98±131.13(6)[b]	94.19±19.29(6)[a]	117.62±36.03(7)	111.96±26.75(7)	72.04±37.80(6)
Control	341.34±230.26(6)	746.65±141.88(6)	256.52±124.97(6)	67.63±29.25(7)	64.35±21.80(6)	65.45±20 .54(6)
Sham-operat.	154.58±38.73(5)[a]	165.35±39.93(4)	148.63±50.78(6)[b]	95.65±28.59(5)	90.51±13.97(4)	9 5.99±34.66(6)

Notes: compared with in control group at the same time, [a]$P<0.05$, [b]$P<0.01$; compared with that in sham-operation group, [c]$P<0.05$, [d]$P<0.01$; (), the number of rats; PGE_2 is not listed because of no significant difference.

Table 2 Comparison of pathologic scores in SD rats with ANP 12hrs after onset ($\bar{x}\pm s$)

Groups	*n*	Edema	Inflammation	Necrosis	Bleeding
Emodin	8	2.62±0.53	2.94±0.32	1.19±1.13[a]	0.25±0.46
Sandostatin	7	2.57±0.34	2.71±1.38	1.28±0.45[b]	0.42±0.53
Control	8	2.56±0.42	3.75±0.53	3.43±0.62	0.63±0.50

Notes: compared with control group, [a]$P<0.05$, [b]$P<0.01$.

DISCUSSION

Rats with taurocholate-induced ANP might simulate human biliary (bile reflux) pancreatitis. The predominant pathophysiological change is severe disturbance of pancreatic microcirculation accompanied by abnormal metabolism of eicosanoids which precedes pancreatic bleeding and necrosis. Pancreas is the main site of the abnormal metabolism of eicosanoids in ANP; after that is the blood (platelet)[1]. TXB_2 and 6-keto-$PGF_{1\alpha}$ are stable metabolites of TXA_2 and PGI_2, respectively. The former is a strong microvascular cons trictor and an agonist of platelet aggregation as well. It can induce deformation, release and secretion of platelets, resulting in local or systemic disorders of coagulation and bleeding. Pancreatic ischemia became worse with complete destruction of pancreatic cytoprotection[2]. Some authors employed selective inhibitors of synthesis of TXB_2, or exotic PGE_2 in rats with ANP, and discovered that the mortality was reduced[3]. These results, together with ours, suggested the role of abnormal metabolites of eicosanoids in the pathogenesis of ANP and possible therapeutic strategies to be adopted. Meanwhile, our study demonstrated that, besides traditional viewpoints, inhibition of abnormal metabolism of eicosanoids, promotion of pancreatic cytoprotection, prevention of coagulation and microth rombosis and improvement of pancreatic microcirculation should also undoubtedly be included in the mechanism of the therapeutic roles of emodin as well as sando statin in the treatment of ANP.

In conclusion, it can be suggested that, the mechanisms of emodin or sandostatin in the treatment of ANP should include modulation of abnormal eicosanoid metabolism and restoration or promotion of pancreatic cytoprotection which might be more important than the well-known “anti-enzyme” or “anti-secretion” speculation.

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