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Effects of quercetin on $Na^{(+)}$-$K^{(+)}$-exchanging ATPase and $Ca^{(2+)}$ $Mg^{(2+)}$-ATPase in rats

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ABSTRACT Quercetin (Que) ig 200 mg·kg^{-1}, qd × 14 d decreased activities of the $Na^{(+)}$-$K^{(+)}$-exchanging ATPase (I) of rat brain plasma membranes and heart sarcolemmal and $Ca^{(2+)}Mg^{(2+)}$-ATPase (II) of heart sarcolemmal membrane. Que 100 mg·kg^{-1} reduced the activity of I from rat heart sarcolemmal prepartion, but had no effect on that from rat brain plasma membranes. The result shows that I of myocardium is more senstive than that of brain in rat. Que also showed a remarkable inhibitory effect in the II of heart sarcolemma.

KEY WORDS quercetin; $Na^{(+)}$-$K^{(+)}$-exchanging ATPase; $Ca^{(2+)}$ $Mg^{(2+)}$-ATPase; myocardium; sarcolemma; brain; cell membrane

The bioflavonoid quercetin (Que), which is widely distributed in plants, decreased the blood pressure and vascular resistance, inhibited platelet aggregation, and had an antiarrhythmic effect[1-4]. Que inhibited the $Na^{(+)}$-$K^{(+)}$-exchanging ATPase (I) purified from the electric organ of electric eel[5], plasma membrane of calf heart[6], and $Ca^{(2+)}$ $Mg^{(2+)}$-ATPase (II) of sarcoplasmic reticulum[7]. In this study, the effects of Que on ATPase I activities of rat brain membrane and heart sarcolemma and on the II activity of heart sarcolemma were investigated to explore its mechanism of action.

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MATERIALS AND METHODS

We purchased Que from Chemical Reagent Factory of Shanghai, ouabain from E Merck, and ATP-Na_2 from Boehringer Mannheim. All other reagents were AR and prepared with tri-distilled water.

Wistar rats (n = 36, ♂) weighing 246 ± s 28 g, were provided by Animal Breeding Center, Suzhou Medical College, and maintained on normal rat chow and tap water ad lib. Rats were randomly divided into 4 groups. The rats were given ig either 0.9 % saline (control group) or Que (50, 100, and 200 mg·kg^{-1}) daily. After 14 d of treatment, the rats were exsanguinated under pentobarbital (ip 40 mg·kg^{-1}) anesthesia. Myocardial membrane fractions[8] and brain plasma membranes[8] were prepared. Membrane protein was quantitated colorimetrically[9], and adjusted to 1 and 0.5 mg protein·ml^{-1} with the medium. All the procedures were carried out below 4 ℃ and the preparation was stored at −20 ℃.

I activity was measured by monitoring the inorganic phosphate released[10]. A final concentration of ouabain 1 mmol·L^{-1} was used as a blank. II activity was assayed[11].

Statistical analysis was carried out with ANOVA.

RESULTS

I activity of rat heart sarcolemma was inhibited by Que dose-dependently. Que 200 mg·kg^{-1} inhibited 77 %. A Que 50 mg·kg^{-1} tended to decrease the activity of the enzyme.

II activity in myocardium of rats treated with Que (100 and 200 mg·kg^{-1}) was significantly lower than that of the control. Que 50 mg·kg^{-1} tended to reduce the II activity.

Que 200 mg·kg^{-1} inhibited I of rat synaptosomal membrane with 34 % of reduction in

enzyme activity. A tendency of decline in the enzyme activity was seen after Que 50 and 100 $mg \cdot kg^{-1}$ (Tab 1).

Tab 1. Effects of Que on $Na^{(+)}$-$K^{(-)}$-exchanging ATPase (I) and $Ca^{(2+)}Mg^{(2+)}$-ATPase (II) in rats. $n=9$, $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ vs saline.

Que/ $mg \cdot kg^{-1}$	I/$\mu mol \cdot Pi \cdot mg^{-1} \cdot h^{-1}$		II/$\mu mol \cdot Pi \cdot mg^{-1} \cdot h^{-1}$
	Brain	Heart	Heart
0	8.1±2.6	16.1±6.0	23±7.1
50	7.1±1.5^a	14.9±5.9^a	22±11.2^a
100	6.9±1.1^a	8.6±5.2^b	16±3.2^b
200	5.3±1.9^b	3.7±1.7^c	15±1.7^c

DISCUSSION

The present work confirmed the inhibitory effects of Que on I and II activities of plasma membrane of myocardium, and on brain synatosomal I activity in rats *in vivo* for the first time, and it was consistent with what was reported *in vitro*[5-7]. And we also found that the I of rat synaptosomal membrane was less sensitively inhibited by Que than rat myocardial enzyme.

Both Que and ouabain could inhibit I activity. However, we have discovered that pretreatment with Que could significantly prevent guinea pigs from the attack of the cardiac arrhythmias induced by ouabain[4]. It seems to be difficult to explain the preventive effects of Que on arrhythmogenic action of ouabain based on their identical inhibitory effects on I, although their models to inhibit I between ouabain and Que are different[5].

Que showed the similar inhibitory action on II. It is generally accepted that II is involved in the outward pumping of Ca^{2+} from the cardiac cells[12], and translocation of Ca^{2+} on the sarcoplasmic reticulum[7], but a real physiological role of the enzyme is not clear[13]. Que may be a useful agent in study of the relationships between the I, II activities and intracellular Ca^{2+} transportation.

REFERENCES

1 Gu ZL, Xie ML, Qian ZN. Effect of quercetin on chemiluminescence of human platelets induced by arachidonic acid. Acta Pharmacol Sin 1993; **14**: 263—5.

2 Gu ZL, Qiao ZN, Xiao D, Zhou YH, Qin ZH, Wang ZY. Inhibitory effects of quercetin on platelet and its mechanism. Acta Acad Med Suzhou 1991; **11**: 262—5.

3 Xiao D, Gu ZL, Qian ZN. Effects of quercetin on platelet and reperfusion-induced arrhythmias in rats. Acta Pharmacol Sin 1993; **14**: 505—8.

4 Xiao D, Gu ZL, Qian ZN. Study on the antiarrhythmic effects of quercetin. Acta Acad Med Suzhou 1993; **13**: 376—8.

5 Kuriki Y, Racker E. Inhibition of (Na^+, K^+) adenosine triphosphatase and its partial reaction by quercetin. Biochemistry 1976; **15**: 4951—6.

6 Carpenedo F, Bortignon C, Bruni A, Santi R. Effect of quercetin on membrane-linked activities. Biochem Pharmacol 1969; **18**: 1495—500.

7 Shoshan V, Maclennan DH. Quercetin interaction with the ($Ca^{2+}+Mg^{2+}$)-ATPase of sarcoplasmic reticulum. J Biol Chem 1981; **256**: 887—92.

8 Jones DH, Matus AI. Isolation of synaptic plasma membrane from brain by combined flotation-sedimentation density gradient centrifugation. Biochim Biophys Acta 1974; **356**: 276—87.

9 Lowry OH, rosebrough NJ, Farr AL, Randall RL. Protein measurement with the folin phenol reagent. J Biol Chem 1951; **193**: 265—75.

10 Jin LQ, Shi L. Effects of saponins of *Panax notoginseng* on sodium - potassium - adenosine triphosphatase and calcium-magnesium-adenosine triphosphatase. Acta Pharmacol Sin 1991; **12**: 504—6.

11 Prasada Rao KS, Chetty CS, Trottman CH, Uzodinma JE, Desaiah D. Effect of tricyclohexylhydroxytin on synaptosomal Ca^{2+}-dependent ATP hydrolysis and rat brain subcellular calmodulin. Cell Biochem Funct 1985; **3**: 267—72.

12 Morcos NC, Drummond GI. ($Ca^{2+}+Mg^{2+}$)-ATPase in enriched sarcolemma from dog heart. Biochim Biophys Acta 1980; **598**: 27—39.

13 Enyedi A, Minami J, Caride AJ, Penniston JT. Characteristics of the Ca^{2+} pump and Ca^{2+} - ATPase in the plasma membrane of rat myometrium. Biochem J 1988; **252**: 215—20.

414－416

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槲皮素对大鼠钠钾腺苷三磷酸酶和钙镁腺苷三磷酸酶的影响

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摘要 槲皮素(Que) ig 200 mg·kg^{-1}，qd×14 d 可显著降低大鼠心肌和脑钠钾腺苷三磷酸酶(I)的活力及心肌钙镁腺苷三磷酸酶(II)的活力；槲皮素100 mg·kg^{-1}降低心肌 I 的活力，但对脑 I 无明显影响. 实验结果提示，大鼠心肌 I 对 Que 的反应较脑 I 敏感；槲皮素也能显著抑制心肌 II 的活力.

关键词 槲皮素；钠$^{(+)}$-钾$^{(+)}$-交换腺苷三磷酸酶；钙$^{(2+)}$-镁$^{(2+)}$-腺苷三磷酸酶；心肌；肉膜；脑；细胞膜

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Comparison of dopexamine hydrochloride, fenoldopam, and procaterol on myocardial nutritional flow in rats[1]

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ABSTRACT Myocardial nutritional flow (MNF) was determined using ^{99m}Technetium-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) in rats. At 25 nmol·kg^{-1}, dopexamine hydrochloride (DH), fenoldopam, and procaterol increased the uptake rate of ^{99m}Tc-MIBI/g myocardium by 80.8±10.2 % ($P<0.01$), 44.9±6.3 % ($P<0.05$), and 30.2±5.4 % ($P<0.05$) respectively. These findings suggested the potential advantages of DH over other dopaminergic agonists in the treatment of coronary disease.

KEY WORDS dopaminergic agents; myocardium; blood flow velocity; technetium Tc 99m sestamibi

Dopexamine hydrochloride (DH), a novel dopamine receptor agonist at both DA_1 dopamine receptors and β_2-adrenoceptors, unlike dopamine, has little β_1-adrenergic activities and does not stimulate vascular α-adrenoceptors[1]. It can improve the cardiac function by reducing afterload and mild positive inotropism without significant increase in myocardial oxygen consumption[2-4]. DH has an anti-arrhythmic action during myocardial ischemia[5]. In an attempt to verify the anti-ischemic action, we evaluated the effect of DH on myocardial nutritional flow (MNF) and made a comparison with fenoldopam (DA_1 dopamine receptor agonist) and procaterol (β_2-adrenoceptor agonist).

MATERIALS AND METHODS

^{99m}Technetium - methoxy - isobutyl - isonitrile (^{99m}Tc-MIBI), supplied by Jiangsu Institute of Atomic Medicine, Wuxi, China, was used. Preparation of the cationic complex of ^{99m}Tc-MIBI was performed by using radioimmunoassay (RIA) reagent kit. The saline eluent of $^{99m}TcO_4^-$ (370 MBq) was added into the ampule containing 1.0 mg methoxy isonitrile cryo-

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