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Inhibitory effects of tetrandrine on Bay k 8644-stimulated contraction of isolated rabbit aortic strips

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ABSTRACT In the presence of KCl 19 mmol · L^{-1}, calcium agonist Bay k 8644 0.47 μmol · L^{-1} elicited a strong contraction of isolated rabbit aortic strips, and this contraction was concentration-dependently inhibited by tetrandrine; but this antagonism was noncompetitive. Calcium ionophore calcimycin evoked contraction was markedly depressed by tetrandrine. The results suggested that tetrandrine might not only inhibit transmembrane influx of calcium via potential-dependent channels but also interfere with other processes related to calcium.

KEY WORDS tetrandrine; dihydropyridines; calcimycin; thoracic aorta

Tetrandrine has vasodilative effect and has been considered as a potential-dependent calcium channel blocker. However, the conclusion was mainly based on experiments using depolarization with high KCl[1,2], which is the "classical" method for testing potential-dependent calcium channels[2,3]. Bay k 8644, a dihydropyridine derivative, is a calcium agonist and has a vasoconstrictive action[4]. In this study, Bay k 8644 as well as calcimycin (A-23187), a calcium ionophore, was used as a vasoconstrictor to examine the vasodilative effects of tetrandrine.

MATERIALS AND METHODS

Tetrandrine was obtained from Jinghua Pharmaceutical Factory in Zhejiang. Bay k 8644 and calcimycin was obtained from Sigma Chemical Co. Bay k 8644 and calcimycin were dissolved in ethanol to an initial concentration of 0.1% and 1% (wt / vol), respectively. All other agents used were AR.

Rabbits (2.2 ± *s* 0.3 kg) of either sex were killed by a sharp blow to the base of the skull. The thoracic aorta was quickly excised, cleaned off fat and connective tissue, and cut into strips approximately 2 mm in width and 20 mm in length. The aortic strips were put in an organ bath containing 20 ml of Krebs buffer (pH 7.3-7.5). The buffer was maintained at 37℃ and gassed continuously with 95% O_2 + 5% CO_2. The contractile responses of aortic strips were isometrically measured by an electro-mechanical transducer connected to a physiological recorder. Resting tension was maintained at 0.5 g and the strips was equilibrated at 37℃ for 90 min before the experiment[5,6].

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RESULTS

Bay k 8644 0.1-4.7 μmol · L^{-1} did not elicit a contraction of the strip in Krebs solution (concentration of KCl : 5 mmol · L^{-1}) (Fig 1). However, it produced a stronger contraction when KCl concentration was elevated to 19 mmol · L^{-1}, while KCl 19 mmol · L^{-1} alone evoked very weak responses (Fig 1). But it was much less effective in increasing the contractile response if concentration of KCl was higher than 40 mmol · L^{-1}.

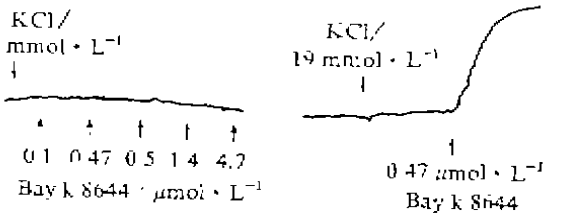

Fig 1. Typical tracings of Bay k 8644-induced contractile responses of isolated rabbit aortic strips in the presence of KCl 5 or 19 mmol · L^{-1}.

Tetrandrine concentration-dependently inhibited the contraction induced by Bay k 8644 in the presence of KCl 19 mmol · L^{-1}. Its IC_{50} value was 62.2 μmol · L^{-1}. But this antagonism was noncompetitive as the dose-response curve to Bay k 8644 was shifted to the right unparallelly and the peak of the curve was markedly lowered in the presence of tetrandrine 40 μmol · L^{-1} (Fig 2). Similarly, calcimycin-evoked contraction was also decreased by tetrandrine. The rate of its inhibition was 62.5% when the strips were pretreated with tetrandrine 160 μmol · L^{-1} for 10 min before addition of calcimycin 20 μmol · L^{-1}.

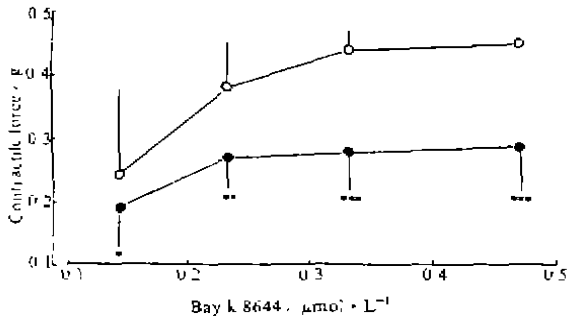

Fig 2. Bay k 8644-induced contraction of isolated rabbit aortic strips under the condition of KCl 19 mmol · L^{-1} in the absence (○) and presence (●) of tetrandrine 40 μmol · L^{-1}. $n=4$, $\bar{x} \pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* group in the absence of tetrandrine.

DISCUSSION

Unlike nifedipine, Bay k 8644 was described as a calcium agonist, which acts directly on the potential-dependent calcium channel to increase the inward calcium current, thereby inducing an increase in vascular contractility[4]. But it had also been reported that a calcium channel agonist alone cannot activate calcium channels and that a moderate depolarizing stimulus is often required[4,5]. The results of our experiments were in accord with these reports. However, the present study confirmed that tetrandrine inhibited vascular contraction induced by Bay k 8644 in the presence of submaximal concentration of KCl and showed that the antagonism was noncompetitive. The results suggested that tetrandrine was unable to compete with Bay k 8644 for dihydropyridine-binding sites in channels.

Unlike Bay k 8644, calcimycin does not activate potential-dependent calcium channels although it can elevate cytoplasmic calcium. It is able to make biologic membranes permeable and allow extracellular calcium to enter into cells if the concentration of extracellular calcium is higher than that of intracellular free calcium[7]. Watson reported that verapamil failed to inhibit cotractions produced by calcimycin in rabbit aorta[7]. But the vasoconstrictive action of calcimycin could be depressed by tetrandrine in our experiments, which suggested that the vasodilative properties of tetrandrine be somewhat different from those of verapamil. The different mechanisms between the two vasoconstrictors, Bay k 8644 and calcimycin, also implied that mechanisms of vasodilation of tetrandrine might be more complicated than supposed to be previously. It might not only inhibit transmembranous influx of calcium via potential-dependent channels but also interfere with other processes related to calcium. However, the mechanism of the processes remains unclear.

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粉防己碱对 Bay k 8644 引起兔离体主动脉条收缩的抑制作用

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提要 在有 KCl 19 mmol · L^{-1} 存在的情况下，钙通道激动剂 Bay k 8644 0.47 μmol · L^{-1} 能诱发兔离体主动脉条产生较强的收缩，而粉防己碱则非竞争性地拮抗这种反应，其抑制作用呈浓度依赖性。粉防己碱对卡西霉素诱发兔离体主动脉条收缩也有明显的抑制作用，但其作用机制尚不清楚。

关键词 粉防己碱；二氢吡啶类；卡西霉素；胸主动脉

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Effects of microinjection of picrotoxin into posterior hypothalamus on ventricular electric stability

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ABSTRACT Ventricular fibrillation threshold (VFT), serum potassium, and monophasic action potentials (MAP) have been assessed before and after microinjection of picrotoxin (Pic) into posterior hypothalamus in rabbits. Pic (2 and 3 μg) brought about a biphasic effect on VFT, an initial decrease followed by a notable increase. Pretreatment with spinal cord transection almost abolished the descending phase, whereas pretreatment with vagotomy depressed the ascending phase significantly. Following the microinjection of Pic, serum potassium rose up to 5.0 mmol · L^{-1} at 30 min. The amplitude of MAP (MAPA) and V_{max} were lessened in rabbits, while in vagotomized rabbits, the changes of MAP were aggravated, and the duration of MAP was shortened. Phentolamine counteracted the changes of MAP induced by Pic.

These results suggested that the initial decrease of VFT caused by Pic derived mainly from the direct action and myocardial ischemia of sympathetic activation, while its subsequent elevation was caused by vagal activation and hyperkalemia.

KEY WORDS picrotoxin; hypothalamus; microinjections, ventricular fibrillation, action potentials; potassium; phentolamine

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Although the arrhythmogenic role of higher CNS activity has been established[1], the neurotransmitters involved therein remain speculative. GABA is now thought to modulate autonomic outflow to cardiovascular system; and enhancement or blockade of central GABAergic neurotransmission with central administration of GABA or picrotoxin (Pic) could inhibit or evoke ventricular arrhythmia, respectively[2,3]. This work will focus on defining the effects of blocking the hypothalamic GABAergic inhibition with Pic on the susceptibility to ventricular fibrillation, the basis of