Effect of MCI-176, a New Calcium Antagonist, on the Calcium Induced Contraction of Isolated Porcine Coronary Arteries

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Abstract—Calcium antagonistic activity of MCI-176, a new calcium antagonist, was compared with those of diltiazem and nifedipine in isolated depolarized porcine coronary arteries. MCI-176, diltiazem and nifedipine competitively inhibited calcium contraction of the large coronary arteries, and their pA₂ values were 7.49, 6.89 and 9.55, respectively. Similar competitive inhibition by MCI-176, diltiazem and nifedipine of calcium contraction was also observed in the small coronary arteries, and their pA₂ values were 7.38, 6.83 and 9.91, respectively. Although calcium antagonistic activity of nifedipine was several hundreds times more potent than MCI-176 and diltiazem, the action of nifedipine, unlike MCI-176 and diltiazem, favored the small coronary arteries rather than the large coronary arteries.

The name “calcium antagonist” is a general term defined from a selective inhibition of the slow calcium influx across the plasma membrane (1). A considerable number of substances fulfilling this criterion are known and have been structurally subdivided into three major groups: dihydropyridine-, verapamil- and diltiazem-type. Recently, the new calcium antagonist MCI-176, 2-(2,5-dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-isopropoxy-4(3H)-quinazolinone hydrochloride, has been synthesized in our laboratory (2). MCI-176 (Fig. 1) is a photostable white crystalline material (molecular weight 461.98) and is easily soluble in water. Structurally, MCI-176 does not belong to the dihydropyridine-, verapamil-, or diltiazem-type. It was of interest to compare the activity of MCI-176 with those of well-known calcium antagonists and to investigate the difference in susceptibilities of coronary arteries with different diameters to these calcium antagonists.

The hearts of adult pigs were obtained from a nearby abattoir and kept in ice cold saline solution. The left coronary artery was carefully dissected out in the oxygenated Krebs-Henseleit solution (NaCl, 118; KCl, 4.7; NaHCO₃, 25; KH₂PO₄, 1.2; MgCl₂, 1.2; CaCl₂, 2.5; and glucose, 11 mM). Ring preparations of the circumflex branch (large coronary arteries, diameter of 3–5 mm) or spiral strips of small branches in the descending branch (small coronary arteries, diameter of 0.1–0.2 mm) were suspended in a 20 ml organ bath maintained at 37°C and aerated with a 95% O₂-5% CO₂ mixture. The preparations were stabilized and contracted with CaCl₂ in the depolarized Krebs-Henseleit solution (NaCl, 43.9; KCl, 80; NaHCO₃, 25; MgCl₂, 1.2; CaCl₂, 2.5; and glucose, 11 mM) in the previously described manner (3). MCI-176 and diltiazem were dissolved in ethanol and successively diluted with distilled water. Nifedipine was originally dissolved in ethanol and successively diluted with distilled water. The final concentration of ethanol was 0.1 ppm, and vehicle effect was negligible. When dealing with nifedi-
pine, the stock solution and the equipment were shielded against room light. Basal tension of 1.5 g and 0.5 g was applied to large and small coronary arteries, respectively. Contraction induced by each concentration of CaCl₂ was expressed as the percentage of the maximal contraction obtained by CaCl₂ before the application of the tested drug. The pA₂ values were calculated according to the method of van Rossum (4), and statistical analyses were performed by the one-way layout of analysis of variance.

CaCl₂ contracted the depolarized large coronary arteries, and the EC50 value for CaCl₂ was 0.25±0.05 mM (N=6) (Fig. 2). In the presence of 0.3 μM of MCI-176, the dose-response curve for CaCl₂ was parallelly shifted to the right by 11.6-fold. The EC50 value for CaCl₂ was 2.85±0.56 mM and the pA₂ value was 7.49±0.09 in the MCI-176 treated group (N=7). Diltiazem (0.3 μM) and nifedipine (1 nM) also exhibited competitive antagonism, and the pA₂ values of diltiazem and nifedipine were 6.89±0.16 (N=5) and 9.55±0.11 (N=4), respectively. Similar experiments were performed in the small coronary arteries (Fig. 2). The small coronary arteries appeared less susceptible to CaCl₂ (EC50=0.44±0.11 mM, N=11) than the large coronary arteries, but no significant difference was detected. MCI-176, diltiazem and nifedipine also inhibited the CaCl₂-induced-contraction competitively in the small coronary arteries, and their pA₂ values were 7.38±0.23 (N=6), 6.83±0.14 (N=6) and 9.91±0.18 (N=7), respectively.

The pA₂ values of nifedipine were significantly greater than those of MCI-176 and diltiazem both in the large and small coronary arteries (P<0.05). The potency ratio of nifedipine to MCI-176 and diltiazem were 115 and 457 in the large coronary arteries and 339 and 1202 in the small coronary arteries. Thus, with regards to the calcium antagonistic activity in the porcine coronary arteries, nifedipine was the most potent. Nifedipine, however, was approximately 2 times less active in the large coronary arteries than in the small coronary arteries, while the effects of MCI-176 and diltiazem were equipotent both in the large and small coronary arteries. In the isolated perfused heart preparation of the dog supported by a donor, among the calcium antagonists only diltiazem produced a dilation of the large conductance coronary artery, and nifedipine and verapamil produced a dilation only of the small resistance coronary artery and arterioles (5). It was also reported that verapamil relaxed the K⁺-induced-contraction rather more sensitively in the small coronary arteries than in the large one, and the difference between the large and small coronary arteries was pharmacologically indicated to be based on the nature of their membrane Ca²⁺ transfer mechanisms (6). In the depolarized porcine coronary arteries, the large vessels seemed to be more sensitive to external Ca²⁺ than the small vessels, but there was no statistically significant difference in the EC50 values. One possibility, however, could be raised that the size of the releasable Ca²⁺ from the Ca²⁺ reservoirs and the overall dependence to the external Ca²⁺ might be different between the large and small coronary arteries. Consequently, the preferential effect of nifedipine to the small coronary arteries might contribute to the generally believed high selective inhibition of
the voltage-dependent influx of Ca++. Another possibility that MCI-176 and diltiazem had an additional action other than the calcium antagonistic effect could not be excluded, because nitroglycerin, differing in the mechanism of action from the calcium antagonists, preferentially dilates the large coronary artery (5, 6).

MCI-176 qualitatively resembled diltiazem, but MCI-176 was revealed to have approximately 4 times superior vasodilative activity. Especially, the pA2 value of MCI-176 was significantly greater than that of diltiazem in the large coronary arteries (P<0.05). Thus it was concluded that MCI-176 would be a beneficial drug for the treatment of ischemic heart diseases.

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