# The antihypertensive and cardioprotective effects of (-)-MJ-451, an ATP-sensitive K+ channel opener.

許準榕

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## Abstract

ATP-sensitive Kq KATP.channelopeners have been shown to be a potentialclass of therapeutic agents for the controlof cardiovascular diseases, including angina, arrhythmias, and hypertension. In this study, the pharmacologicalactivity of 6-cyano-3S,4R-dihydro- 2,2-dimethyl-2H-3-hydroxy-4-w5S- 1-hydroxymethyl-2-oxo-1-pyrrolidinylx-1-benzopyran y.-MJ-451., a synthetic KATP opener, was evaluated in anesthetized rat models and in isolated rat thoracic rings. Results demonstrated that intravascular injection ofy.-MJ-451 0.02, 0.05 and 0.1 mgrkg. produced an immediate, dose-related reduction in mean arterialblood pressure in anesthetized spontaneously hypertensive rats SHR., which persisted for more than 3 h and was not accompanied by reflex tachycardia. The hemodynamic changes were completely abolished by pretreatment with glibenclamide 4 mgrkg, i.v. bolus., a selective KATP channelblocker. In isolated thoracic aorta, y.-MJ-451 10 nM-3 mM. produced a concentration-dependent vasodilator effect on the phenylephrine 0.3 mM.-induced vasoconstriction. Moreover, y.-MJ-451 relaxed the thoracic aorta contracted by low 5, 20 and 30 mM., but not high 40 and 60 mM. concentrations of extracellular potassium. In addition, y.-MJ-451 showed cardioprotective effects in the rat modelof 45-min left coronary artery occlusion followed by 1-h reperfusion. In myocardialischemia, pretreatment with y.-MJ-451, 5 and 10 mgrkg, i.v. bolus.significantly reduced the incidence of ventricular fibrillation and the mortality, also reducing the totalnumber of ventricular premature contractions, totalduration of ventricular tachycardia and ventricular fibrillation. A significant reduction in infarct size was noted in three y.-MJ-451 2, 5 and 10 mgrkg.-treated groups. Also, the cardioprotective effects ofy.-MJ-451 were virtually abolished by pretreating the rats with glibenclamide 4 mgrkg, i.v. bolus.. In conclusion, y.-MJ-451, through opening the KATP channel, exerted antihypertensive and cardioprotective effects. Therefore, it is suggested that y.-MJ-451 has potential in the treatment of hypertension or acute myocardialinfarction. q2000 Elsevier Science B.V. All rights reserved.