P275

ADTM, a synthetic dimer of Danshensu and tetramethylpyrazine, induces relaxation in rat mesenteric arteries

RWS Li[1], Y Wang[2], SMY Lee[3], SW Chan[4], YW Kwan[5], GPH Leung[1]. *[1]The University of Hong Kong, Department of Pharmacology and Pharmacy, Hong Kong, [2]Jinan University, Institute of New Drug Research 510000, China, [3]University of Macau, Institute of Chinese Medical Sciences, Macao, [4]The Hong Kong Polytechnic University, State Key Laboratory of Chinese Medicine and Molecular Pharmacology, Department of Applied Biology and Chemical Technology, Hong Kong, [5]The Chinese University of Hong Kong, School of Biomedical Sciences, Hong Kong*

Danshen (Radix salviae miltiorrhizae) and ChuanXiong (Ligusticum wallichii) are two traditional herbal medicines commonly used in the treatment of cardiovascular diseases in China. The active components in Danshen and ChuanXiong are Danshensu (DSS, (R)-3, 4-dihydroxyphenyllactic acid) and tetramethylpyrazine (TMP), respectively. We have recently synthesized a new compound named as ADTM which is basically a synthetic dimer of DSS and TMP. In this study, the effect of ADTM on the contractility of rat mesenteric arteries was examined.

Male Sprague-Dawley rats (10-12 weeks old) were used in this study. Their mesenteric arteries were isolated for the measurement of isometric tension. The incubation time of antagonists or drugs was 30 minutes. The results showed that ADTM caused a dose-dependent relaxation in rat mesenteric arteries. ADTM induced a significantly stronger vasorelaxation than DSS, TMP and when DSS and TMP were used together. The ADTM-induced relaxation was endothelium-independent. Consistently, ADTM-induced vasorelaxation was not attenuated by L-NAME (a nitric oxide synthase inhibitor) and ODQ (a soluble guanylyl cyclase inhibitor). In addition, adenylate cyclase/cAMP pathway was not involved in the ADTM-induced relaxation as SQ 22536 (an adenylate cyclise inhibitor) did not alter the relaxation. Potassium channels was not involved in the ADTM-induced vasorelaxation since iberiotoxin (a big conductance Ca2+-activated K+ channel blocker), glibencalmide (a ATP-sensitive K+ channel blocker), 4-aminopyridine (a voltage-activated K+ channel blocker), barium chloride (an inward rectifier K+ channel blocker) and tetraethylammonium (a non-specific K+ channel blocker) did not alter the ADTM-induced vasorelaxation. Interestingly, the potassium chloride (KCl)-induced and calcium chloride (CaCl2)-induced contractions were suppressed by the preincubation of 100μM ADTM. The KCl-induced and the CaCl2-induced contraction was decreased by 65.6±4.0% ($p<0.001$, $n=6$) and 43.4±4.1% ($p<0.001$, $n=6$) when compared with control respectively, suggesting that ADTM might work through the inhibition of Ca2+ influx into the vascular smooth muscle cells.

In conclusion, our study demonstrated that ADTM is a novel vasodilator which is stronger than its analogues DSS and TMP. ADTM may serve as a blocker of Ca2+ channels, resulting in the decrease in Ca2+ influx and hence causing the relaxation of vascular smooth muscle.