Antihypertensive and hypolipidemic effects of DC-015, a novel potent and selective a1-adrenoceptor antagonist comparison with prazosin in spontaneously hypertensive rats.

許準榕

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Abstract

The hypotensive effect of DC-015, a newly synthesized quinazoline derivative, was investigated and compared with prazosin in spontaneously hypertensive rats (SHR). Intravenous administration of DC-015 and prazosin (both at 0.01, 0.05 and 0.1 mg/kg) induced a dose-dependent reduction of mean arterial pressure (MAP) which reached a maximal effect at 5 min after injection and persisted over 2 h in SHR. Furthermore, at higher doses DC-015 (0.1 mg/kg i.v. and 2.0 mg/kg orally, respectively) did not cause any significant changes in heart rate (HR); whereas the same doses of prazosin (0.1 mg/kg i.v. and 2.0 mg/kg orally, respectively) produced a decrease in HR which seems to parallel the time course of the hypotensive response in SHR. DC-015 and prazosin attenuated pressor responses to phenylephrine (10 μg/kg) but failed to inhibit the pressor effects of angiotensin II (0.5 μg/kg) even at the maximal hypotensive dose (0.1 mg/kg). This observation indicates that DC-015 appears to exert its hypotensive effect through 1-adrenoceptor blockade. On the other hand, in SHR fed a high-fat-high-cholesterol (HF-HC) diet, oral administration of DC-015 and prazosin (both at 1.0 mg/kg, twice a day) for 4 weeks caused significant reductions in total plasma cholesterol (CE), low-density lipoprotein (LDL)-cholesterol and total plasma triglyceride (TG). DC-015 therapy also increased high-density lipoprotein (HLD)-cholesterol levels, thus the ratio of total plasma cholesterol to HDL-CE was improved. In contrast, prazosin did not significantly increase the HDL-CE level in this study. It is concluded that DC-015 decreased MAP, plasma CE, LDL-CE, plasma TG and increased HDL-CE levels. DC-015 may have therapeutic potential as a potent antihypertensive drug via the 1-adrenoceptor antagonist. Concurrently, DC-015 may thus hold some advantage for the reduction of two of the major risk factors, hypertension and hyperlipidemia, for cardiovascular diseases.