

Abstract

Evidence is mounting that endothelin (ET)-1 has proatherogenic properties. This is supported by finding that selective ETA receptor antagonists reduce atherosclerotic lesions in animals. However, we recently demonstrated that there is an increased immunoreactivity of ET-1 and ETB receptors in human and mouse atherosclerotic lesions. To examine additional effects of ETB receptor antagonism on atherogenesis, we investigated the chronic effect of the non-selective ETA/ETB receptor antagonist SB209670 on the development of atherosclerosis in apolipoprotein E (apoE)-deficient mice. 94 male mice (10 weeks of age) were randomly divided into four groups: Mice fed a Western-type diet or a chow diet with SB209670 treatment (10mg/kg/day) or placebo for 12 weeks. In mice fed the Western-type diet, but not in mice fed the chow diet, treatment with SB209670 significantly attenuated the increase of plasma total cholesterol level predominantly in very low density lipoprotein and intermediate density lipoprotein fractions without altering the plasma triglyceride level. Furthermore, treatment with SB209670 significantly reduced the extent of aortic atherosclerosis by 53% in mice fed the Western-type diet, and by 38% in mice fed the chow diet. Histological analysis revealed that SB209670 protected the formation of atheromatous plaque lesions by inhibiting the fibroproliferative process. We found that chronic administration of SB209670 reduced diet-induced hypercholesterolemia and atherosclerosis in apoE-deficient mice. ET-1 acting through the ETB in addition to ETA receptor may play an important role in atherogenesis. Non-selective ETA/ETB receptor antagonists may have a therapeutic potential in human atherosclerotic disease.