performed with the use of StatView J-4.5 software (Abacus concepts). Data in Table 1 and Fig.1 were analyzed by repeated measure ANOVA. If significance was detected, differences between groups were analyzed for each experimental period by one-way ANOVA followed by Scheffe's F test. Data in Fig.3 were analyzed by one-way ANOVA followed by Scheffe's F test. Aortic lesion area was analyzed by the Kruskal-Wallis test followed by Mann-Whitney's U test between two groups. A value of $P < 0.05$ was considered significant.

3. Results

3.1 Blood pressure.

Table 1 shows the periodical change in systolic blood pressure during the study. Systolic blood pressure did not differ between the groups, and was not affected by chronic SB209670 treatment.

3.2 Plasma lipid levels and body weight.

A Western-type diet resulted in marked increases in the plasma total cholesterol, triglycerides and body weight. (Fig.1abc). In mice fed the Western-type diet, SB209670 significantly reduced the plasma total cholesterol level (1079.7 ± 74.5 vs. 1503.1 ± 101.4 mg/dl, $P < 0.001$, at the end of the experiment, Fig.1a) and body weight (44.6 ± 1.4 vs. 52.0 ± 1.5 g, $P < 0.001$, Fig.1c) without altering the plasma triglyceride level (133.2 ± 10.7 vs. 130.6 ± 12.3 mg/dl, Fig.1b) compared with control mice. However, on a chow diet, plasma lipid levels (448.6 ± 15.6 vs. 468.8 ± 23.8 mg/dl in total cholesterol level, 81.7 ± 7.4 vs. 78.5 ± 6.0 mg/dl in triglyceride level) and body weight (36.2 ± 0.6 vs. 35.1 ± 0.8 g) were no different between the groups (Fig.1abc).

3.3 Plasma lipoprotein profiles.

To evaluate whether differences in the lipid composition of SB209670-treated mice existed, we examined lipoprotein profiles. As shown in Fig.2a, apoE-deficient mice basically showed a broad β band on agarose gel electrophoresis of whole plasma. In SB209670-treated mice fed the Western-type diet, β migrating remnant particles were markedly reduced compared with in control mice. However, on the chow diet, there was little difference between mice with and without SB209670 treatment. Further, in mice on the Western-type diet, the distribution of cholesterol among the lipoprotein fractions was determined by sequential ultracentrifugation[43]. As shown in Fig.2b, the cholesterol level in VLDL and IDL fractions was markedly reduced in SB209670-treated mice compared with control mice.

3.4 Aortic ET-1 content, plasma ET-1 and NOx.

Both groups of SB209670- treated mice showed less aortic ET-1 content (1.09 $\pm$ 0.13 vs. 2.97 $\pm$ 0.28 pg/mg tissue, on the Western-type diet; 1.27 $\pm$ 0.11 vs. 2.35 $\pm$ 0.14 pg/mg tissue, on the chow diet) and a higher plasma ET-1 concentration (2.98 $\pm$0.11 vs. 2.35$\pm$0.13 pg/ml, on the Western-type diet; 2.20 $\pm$ 0.08 vs. 1.52 $\pm$ 0.13 pg/ml, on the chow diet) than the respective controls. (Fig.3ab). Moreover, plasma NOx of SB209670-treated mice was significantly higher than control in both diet groups (13.2 $\pm$ 0.95 vs. 9.24 $\pm$ 0.55 μM, on the Western-type diet; 17.7 $\pm$ 1.06 vs. 10.7 $\pm$ 0.99 μM, on the chow diet, Fig.3c).

.3.5 Quantification of atherosclerosis.

The severity of aortic atherosclerotic lesions was quantified by measuring the sudanophilic area of the aorta. As shown in Fig.4ab, control mice on the Western-type diet developed atherosclerotic lesions that were significantly larger than those observed in controls on the chow diet (22.6 $\pm$ 0.8% vs. 12.9 $\pm$

0.9%, P <0.0001). This effect was also observed in SB209670-treated mice (10.6 ± 0.9% vs. 8.0 ± 0.6%, P <0.05). Treatment with SB209670 reduced atherosclerosis by 53% in mice fed the Western-type diet (P <0.001), and by 38% in mice fed the chow diet (P <0.001). Furthemore, the lesion area observed in SB209670-treated mice fed the Western-type diet was similar to that found in control mice fed the chow diet, which probably indicates that the exacerbating effect of the Western-type diet is quantitatively similar to the preventative effect of SB209670 treatment and suggests that the effect is independent of the plasma cholesterol level. And the lesion morphology of the aortic arch was affected by SB209670 treatment: control mice fed a Western-type diet predominantly showed fibrofatty plaques or atheromas, whereas SB209670-treated mice preferencially showed fatty streak lesions or intermediate lesions, and fibrous caps were rarely seen (Fig.4c). However, on the chow diet, SB209670 had no effect on plaque morphology: their lesions were similar to those of SB209670-treated mice on the Western-type diet (data not shown).

4. Discussion

To examine additional effects of ETB receptor antagonism on atherogenesis, we examined the effect of the non-selective endothelin receptor antagonist SB209670 (35-37) on atherosclerotic lesions in apoE-deficient mice, a suitable animal model of atherosclerosis (38-41), because systemic administration of selective ETB receptor antagonists leads to adverse effects such as hypertension and increased peripheral vascular resistance (33,34). The vasoconstrictor effects of ETB antagonism have been shown to result directly from blockade of an endothelial ETB receptor-mediated dilator tone or indirectly from displacement of endogeneously generated ET-1 to vasoconstrictor ETA receptors, or as a result