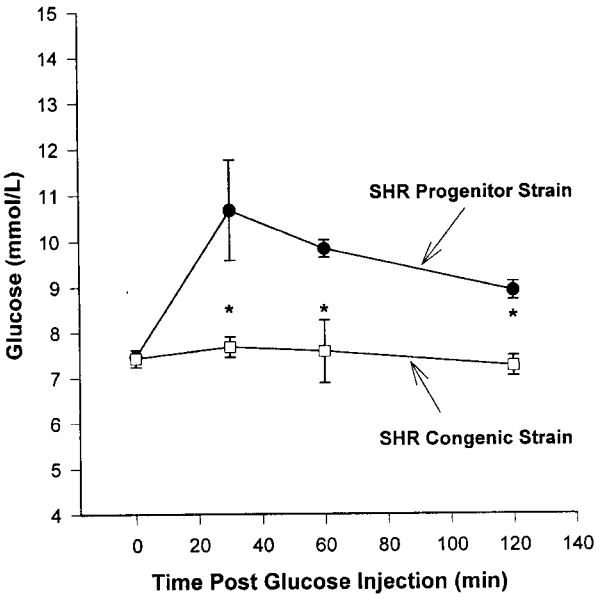

Fig. 4. Glucose tolerance test results in the SHR progenitor strain (n = 9) and the SHR-4 congenic strain (n = 6). Serum glucose levels were significantly higher in the SHR progenitor strain than in the SHR-4 congenic strain at 30, 60, and 120 min after glucose loading (*, $P < 0.05$).
Reproduced with permission, Journal of Clinical Investigation.

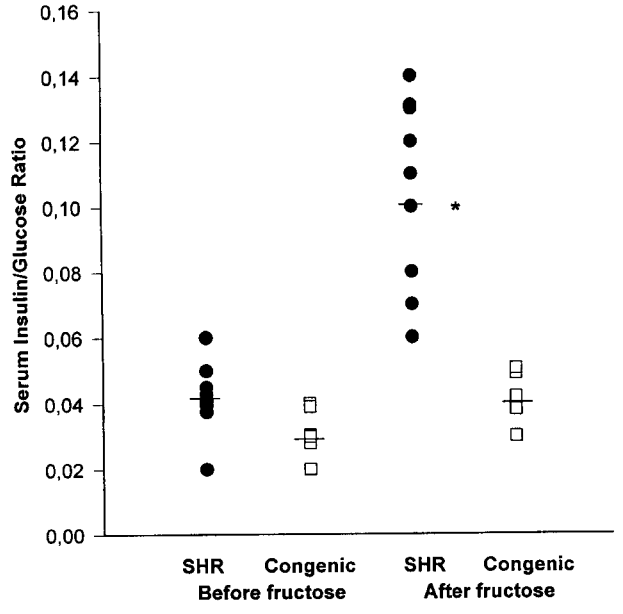

Fig. 5. Scatter plot showing serum insulin/glucose ratios in SHR progenitor (n = 9) (solid symbols) versus SHR-4 congenic rats (n = 6) (open symbols) before and after 15 days on a high-fructose diet. Horizontal bars denote group means. After fructose feeding, insulin/glucose ratios were significantly higher in the SHR progenitor strain than in the SHR-4 congenic strain (*, $P < 0.001$).
Reproduced with permission, Journal of Clinical Investigation.

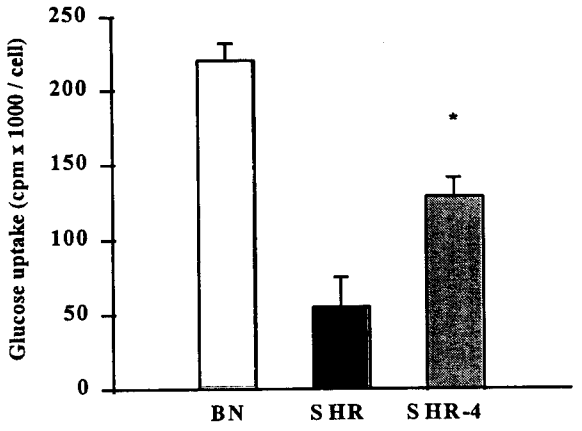

Fig. 6. Insulin-mediated glucose uptake in isolated adipocytes was significantly greater in the SHR-4 congenic strain than in the SHR progenitor strain (*, $P < 0.05$).

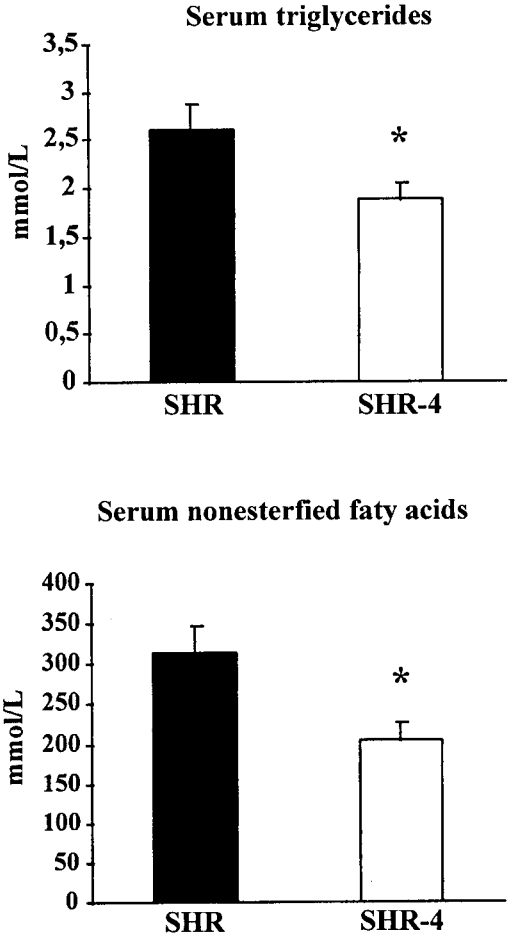

Fig. 7. Lipid profiles in SHR progenitor and SHR-4 congenic strains fed a diet with 60% of fructose for 15 days: serum levels of triglycerides and nonesterfied fatty acids were significantly decreased in the SHR-4 congenic strain when compared to the SHR progenitor (*, $P < 0.05$).

confirmed that the SHR progenitor strain harbors a major deletion in Cd36, which abolished expression of the encoded protein and was responsible for the SHR abnormalities in fatty acid transport and increased circulating levels of fatty acids and triglycerides (Aitman et al., 1999; Pravenec et al., 1999).

Cd36 belongs to scavenger receptors that mediate binding and uptake of native and modified lipoproteins by macrophages. Recently, Cd36 has been shown to be involved in accumulation of lipids in macrophages as a result of exposure to oxidized low-density lipoproteins (LDL) and through induction of the peroxisome proliferator-activated receptor γ (PPARγ). There is a mounting evidence implying a role for Cd36 in normal lipid metabolism as a key protein of the transmembrane transport of fatty acids (Febraio et al., 1999; Ibrahimi et al., 1999).

Metabolic effects of Cd36 deletion and overexpression in the mouse – comparison with SHR

Recently, Febbraio et al. (1999) described the generation by homologous recombination of mice null in the Cd36. These mice produced no detectable Cd36 protein. Cd36-null mice, like SHR carrying a spontaneous deletion in Cd36, show significantly increased levels of circulating fatty acids, HDL cholesterol, and triglycerides. On the other hand, null mice had lower fasting serum glucose levels when compared to controls and showed no obvious evidence of insulin resistance.

To directly assess the role of Cd36 in mediating *in vivo* uptake of fatty acids in muscles, Ibrahimi et al. (1999) have generated a transgenic mouse with overexpression of Cd36 specifically in muscles. These transgenic mice had slightly lower body weight with less adipose tissue, exhibited a greatly enhanced ability to oxidize fatty acids in muscles, had lower blood levels of triglycerides and fatty acids and a reduced triglyceride content in the very low-density lipoproteins (VLDL) subfraction. Blood HDL cholesterol levels were slightly lower. Blood glucose was significantly increased, while insulin levels were similar in the fed state and higher in the fasted state. However, glucose tolerance was similar in control and transgenic mice (Table 1). These studies in null and transgenic mice proved an important *in vivo* role of Cd36 in facilitated cellular fatty acid uptake and its importance to overall fatty acid metabolism.

Since most SHR strains that descend from the SHR colony at the National Institutes of Health (NIH) carry multiple mutations in Cd36 and have no detectable Cd36 protein product in adipose and muscle tissues, they can be considered "natural" Cd36-null strains (Aitman et al., 1999). Table 1 demonstrates that the SHR exhibits similar lipid abnormalities as the Cd36-null mice and that the

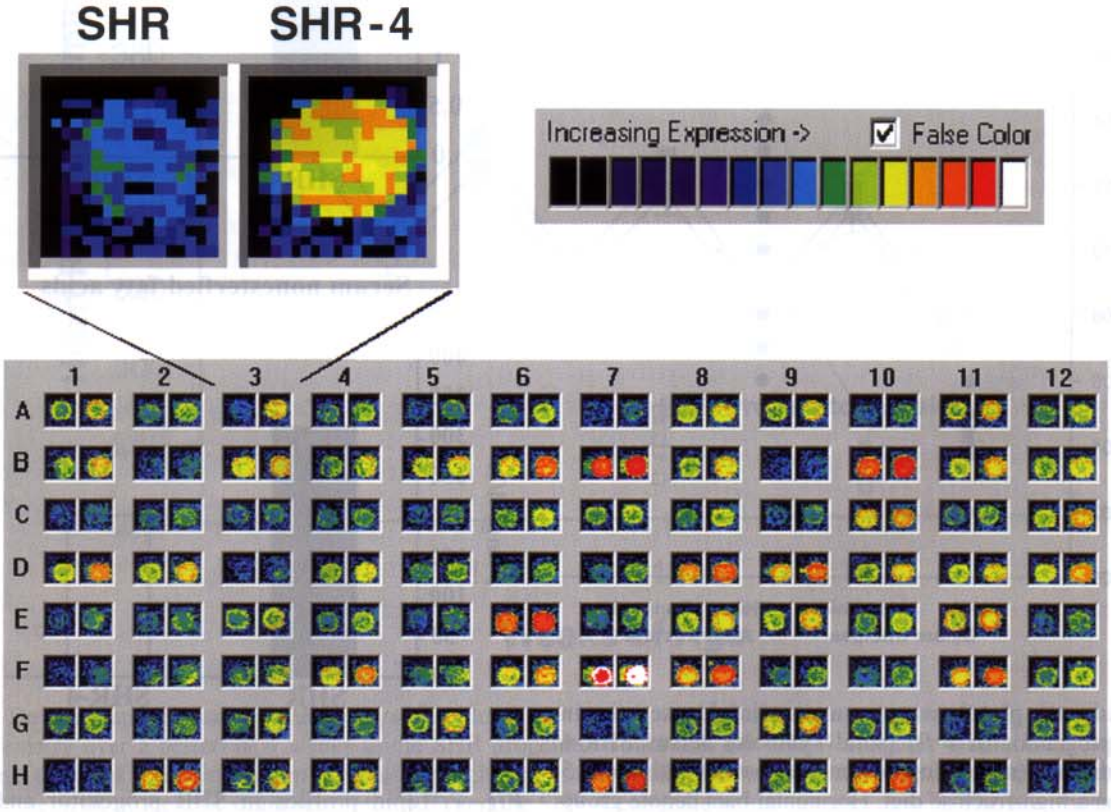

Fig. 8. cDNA microarray analysis of fat tissue in SHR progenitor and SHR-4 congenic strains. Expression data for 96 clones, out of approximately 10,000 individual rat cDNA clones, are shown. Hybridization signals of a Cd36 clone in SHR versus SHR-4 are shown in a magnified view.