Aim: Evidences have suggested that the endocannabinoid system is overactive in obesity, resulting in enhanced endocannabinoid levels in both circulation and visceral adipose tissue. The cannabinoid CB1 receptor is expressed in the adipose tissue besides the brain. The blockade of cannabinoid receptor type 1 (CB1) has been proposed for the treatment of obesity. Besides loss of weight, the CB1 antagonism improves insulin sensitivity, in which the glucose transporter GLUT4 plays a key role. The objective of the present study was to investigate the CB1 receptor modulation on glucose transporter GLUT4 expression, which is encoded by the Slc2a4 gene, and the related transcriptional mechanisms. Methods and Results: 3T3-L1 adipocytes were incubated in the presence of a selective antagonist of CB1 receptor, AM251 [1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl-1H-pyrazole-3-carboxamide]. After 2 or 24 hours, cells were harvest to evaluate GLUT4 mRNA (Real Time PCR) and protein (Western blotting), and NF-kappaB and SREBP-1 activation specifically on the promoter of Slc2a4 gene (EMSA). It was found that acute and chronic incubation for 2 or 24 hours with AM 251 expressively increased GLUT4 protein content (P<0.001) but did not altered GLUT4 mRNA expression. Moreover, increased GLUT4 mRNA expression was only observed after 2 hours of AM 251 treatment (P<0.001). Finally, the binding activity of NF-kappaB decreased after 2 or 24 hour-incubation, while the binding activity of SREBP-1 increased after 24 hour-incubation. Conclusion: These findings reveal that the blockade of CB1 receptor markedly increases Slc2a4/GLUT4 expression in adipocytes, a feature that involves NF-kB and SREBP-1 transcriptional regulation. FAPESP (08/09194-4 and 07/50554-1)