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Overexpression of GLUT2/ Slc2a2 are accompanied by Hnf-1α, Hnf-4α and Hnf-3β transcriptional regulation in liver of Nonalcoholic steatohepatitis obese diabetic mice

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Background and aims: Glucose transporter GLUT2 encoded by Slc2a2 gene plays a key role in glycemic homeostasis. The non-alcoholic steatohepatitis (NASH) is associated with insulin resistance, diabetes and obesity, situations that could induce alteration of expression of GLUT2/Slc2a2. We believe that GLUT2/Slc2a2 can be involved in the development NASH that is accompanied by over expression of the transcriptional factors Hnf-1α, Hnf-4α and Hnf-3β. Considering the importance of knowing the glucose flux in liver of obese diabetic animals with non-alcoholic steatohepatitis, we studied the expression of GLUT2, Slc2a2, G6Pase, PEPCK, GK, Hnf-1α, Hnf-4α and Hnf-3β.

Materials and methods: We studied obese (MSG) and control (C) mices. The obesity was induced by neonatal subcutaneous dose of monosodium glutamate (2 mg/g) during 5 days and a higher dose (4 mg/g) at the 7th day of life. After the weaning, the animals were fed with normal (ND) and high fat diet (HD-60% of fat) by 16 weeks. For determination of NASH, the paraffin-embedded liver was stained by regular hematoxylin-eosin (HE) method for evaluation of liver histology (hepatocellular steatosis, ballooning and inflammation). We obtain four groups: MSG-ND, MSG-HD, C-ND and C-HD. The obesity is not always related with high weigh, thus measures of adiposity, Lee index and weigh of periepididymal adipose should be used. The GLUT2 expression was analyzed by Western blotting; Slc2a2, G6Pase, PEPCK, GK, Hnf-1α, Hnf-4α and Hnf-3β expression was analyzed by Real time-PCR, respectively). The Hnf-1α, Hnf-4α and Hnf-3β binding activity of nuclear protein into Slc2a2 promoter was analyzed by Eletrophoretic Mobility Assay.

Results: The histological analyses state that non-alcoholic steatohepatitis is present in MSG-HD mices fed by 16 weeks. The MSG (ND and HD) mices showed: hyperglycemia and a high level of blood cholesterol ($P<0.05$) when compared with C (ND and HD) group. In comparison to all groups, the MSG-HD showed higher weigh ($P<0.05$) and also higher Lee index ($P<0.01$). The weight of periepididymal adipose was higher in MSG-HD group when compared to C-ND and C-HD groups ($P<0.01$). In comparison to C-ND and C-HD animals, MSG-ND and MSG-HD mices showed increased GLUT2 content ($P<0.05$). The Slc2a2 mRNA is increased in MSG-HD compared with all groups ($P<0.05$). Similar, G6Pase, PEPCK, Hnf-1α, Hnf-4α and Hnf-3β mRNA are increased in MSG-HD compared with C-ND ($P<0.05$). The expression of GK mRNA is decreased in MSG-HD and MSG-ND compared to C-ND and C-HD groups D ($P<0.05$). In comparison to C-ND and C-HD animals, MSG-ND and MSG-HD mices showed increased Hnf-1α, Hnf-4α and Hnf-3β bindig activity of nuclear protein into Slc2a2 promoter ($P<0.05$)

Discussion and conclusions: We demonstrated that, treatment of monosodium glutamate associated with high fat diet by 16 weeks leads to NASH. NASH is related to insulin resistance where there is a high output of fatty acids and glucose to the liver. This glucose can be converted into triglycerides by the de novo lipogenesis contributing for the hepatic steatosis. Thus, there is a higher influx of glucose, demonstrated by increased mRNA expression of G6Pase, PEPCK and Hnf-1α, Hnf-4α and Hnf-3β decreased mRNA expression of GK, where over expression of GLUT2/ Slc2a2 can collaborate to NASH by facilitate the glucose input to hepatocyte.

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