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Transcriptional Regulation of the Genes Related to Lipid Metabolism through Amino Acid Uptake Mediated by the Na^+ - Dependent Glutamine Transporter

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Summary

Glutamine is the most abundant amino acid in stream and involves in many cell function through modulation of various signaling pathway. In the present study, we have demonstrated that glutamine stimulates HMG-CoA (3-hydroxy-3-methylglutaryl CoA) synthase mRNA levels, known as SREBP target genes. Glutamine also up-regulated the expression of SREBPs mRNA, including SREBP-1a, SREBP-1c, and SREBP-2. Glutamine mediated induction of SREBP-1c and SREBP-2 mRNA levels was attenuated while glutamine mediated induction of SREBP-1a mRNA level was not changed by the treatment with sterols, that suppresses SREBP processing. The expression of SREBP-1a mRNA, a predominant form of SREBP-1 in most cultured cells and a target of the general transcription factor Sp1, is significantly augmented by an increase in glutamine-induced O-glycosylation of Sp1. In contrast, the increased expression of SREBP targets, including SREBP-1c and SREBP-2, is due to a stimulation of the processing of SREBP proteins by glutamine. Moreover, time-course experiments demonstrated that glutamine increased the amount of mature SREBP-1 and SREBP-2 prior to the induction of transcription levels.

The transport of glutamine into HepG2 cells via a sodium-dependent transporter causes an osmotic swelling of the cells. Since alanine and prorine were also transported into HepG2 cells via a sodium-dependent transporter, we tested the effect of these amino acids on SREBP processing. While 20 mM glutamine treatment stimulated SREBP processing, same concentration of alanine or proline treatment did not influence SREBP processing, implying that osmotic change dose not involved in the stimulation of SREBP processing by glutamine.

In conclusion, the present study shows that the treatment of glutamine in HepG2 cells causes stimulation of SREBP-1a mRNA expression, which seems to be mediated by the activation of HBP. Furthermore, posttranslational processing of SREBP-1 and SREBP-2 is independently stimulated by the treatment of glutamine through distinct signaling pathway. The remaining question to be clarified is how glutamine stimulates transport of SREBP/SCAP complex from ER to Golgi. The molecular mechanism of this effect is now under investigation.