Amino acid starvation induces glycine transporter 1 gene expression.

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Glycine is a co-agonist at NMDA receptors and an agonist at glycine receptors. Glycine transporters reuptake glycine from the synaptic cleft and regulate glycine concentration. Glycine transporter subtype 1 (GlyT1) is abundant in astrocytes and GlyT1 inhibitors have analgesic effect. We found that GlyT1 mRNA expression in C6 glioma cells was increased during amino acid starvation. To investigate the mechanisms underlying GlyT1 mRNA upregulation, we focused on ATF4 (activating transcription factor 4) that is activated during amino acid starvation and mTOR (mammalian target of rapamycin) that is inactivated during amino acid starvation. Tunicamycin, an ER stress inducer that upregulates ATF4 expression, led to increase of GlyT1. Next, we examined the involvement of mTOR in GlyT1 expression. The mTOR inhibitor rapamycin increased GlyT1 mRNA expression in the culture medium with amino acids. Moreover, ATF4 mRNA expression was also increased by rapamycin. These results indicate that ATF4 increases GlyT1 and mTOR downregulates GlyT1 gene expression.