Abstract

Hypoxia inducible factor-1α (HIF-1α) is a key transcription factor that maintains oxygen homeostasis. Hypoxic stress is related to the pathogenesis of amyotrophic lateral sclerosis (ALS), and impaired HIF-1α induces motor neuron degeneration in ALS. Dimethyloxalylglycine (DMOG) upregulates the stability of HIF-1α expression and shows neuroprotective effects, but has not been used in ALS as an anti-hypoxic stress treatment. In the present study, we investigated hypoxic stress in ALS model mice bearing G93A-human Cu/Zn superoxide dismutase by in vivo HIF-1α imaging, and treated the ALS mice with DMOG. In vivo HIF-1α imaging analysis showed enhanced hypoxic stress in both the spinal cord and muscles of lower limbs of ALS mice, even at the pre-symptomatic stage. HIF-1α expression decreased as the disease progressed until 126 days of age. DMOG treatment significantly ameliorated the decrease in HIF-1α expression, the degeneration of both spinal motor neurons and myofibers in lower limbs, gliosis and apoptosis in the spinal cord. This was accompanied by prolonged survival. The present study suggests that in vivo bioluminescence resonance energy transfer (BRET) HIF-1α imaging is useful for evaluating hypoxic stress in ALS, and that the enhancement of HIF-1α is a therapeutic target for ALS patients.

Key words: ALS, hypoxic stress, in vivo imaging, HIF-1α, DMOG