Respiratory Motor Neuron Death in ALS: Enhanced Plasticity in Surviving Phrenic Motor Neurons by an ERK Dependent Mechanism

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Abstract

Phrenic motor neuron survival (~40%) and output (~50%) are decreased in rats with amyotrophic lateral sclerosis (ALS; SOD1G93A) at end-stage. Thus, we wanted to investigate if we could improve phrenic output by inducing plasticity. Phrenic long-term facilitation (pLTF; a form of respiratory plasticity) is elicited after acute intermittent hypoxia (AIH) (3, 5 minute 11% O2 exposures) and is dependent on Gq metabotropic coupled receptors and MEK/ERK, which we term the “Q” pathway. Gs coupled metabotropic receptors and PI3K/Akt, which we term the “S” pathway, also can contribute to pLTF. Importantly, enhanced pLTF is exhibited in a rodent model of ALS (SOD1G93A rats). However, the mechanism for enhanced pLTF in SOD1G93A rats is unknown. To understand the mechanisms involved in this enhanced pLTF, we studied AIH-induced pLTF after intrathecal delivery of inhibitors for MEK/ERK (U0126) or PI3 kinase/Akt (PI828) in SOD1G93A end-stage rats. In addition, phrenic motor neuron survival was quantified in SOD1G93A rats in order to confirm that enhanced pLTF is a result of plasticity exhibited by surviving phrenic motor neurons and not from reductions in phrenic motor neuron death. UO126 blocked pLTF in wild-type (1±7%; n=8; p<0.05) and SOD1G93A rats (7±2%; n=8; p<0.05), whereas PI828 had no effect in either group (wild-type: 53±6%; n=8; SOD1G93A: 128±23%; n=8; p>0.05). These results reveal that enhanced pLTF in SOD1G93A rats is dependent on the “Q” pathway. Phrenic motor neuron survival in SOD1G93A rats was significantly decreased compared to age-matched wild-type littermates in all treatment groups (p<0.001), verifying that plasticity was a result of surviving phrenic motor neurons and not that less phrenic motor neurons were dying (i.e. phrenic motor neuron death is similar to previous generations). Our results increase understanding of respiratory plasticity and its potential to restore breathing capacity during ALS.