Respiratory motor neuron death in ALS: enhanced plasticity in surviving phrenic motor neurons by a BDNF synthesis-dependent mechanism

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative motor neuron disease that leads to muscle paralysis, and inevitably death from respiratory failure. Ideally, if motor neuron degeneration could be rescued, or motor output enhanced, the quality of life in ALS patients may be preserved. Since the respiratory system is necessary for survival, understanding the mechanisms that control it is important, especially in ALS patients. Phrenic motor neurons send their output via the phrenic motor nerve which then innervates the diaphragm and is important for respiration. It has been shown that phrenic motor neurons exhibit plasticity after exposure to acute-intermittent hypoxia (AIH; 3 episodes of 11% O₂, separated by normoxia) which is termed phrenic long-term facilitation (pLTF). AIH-induced pLTF is dependent on Gq metabotropic coupled receptors and new BDNF synthesis (termed the Q pathway), although Gs metabotropic coupled receptors and new TrkB synthesis (termed the S pathway) can contribute. Importantly, enhanced pLTF is exhibited in a rodent model of ALS (SOD1G93A rats). However, the mechanism for enhanced pLTF in SOD1G93A rats is unknown. Here, we studied whether enhanced pLTF in SOD1G93A rats is due to enhancement of the Q pathway or if the S pathway has increased contribution. To address this question, small interfering RNA (siRNA) directed against BDNF and TrkB were delivered intrathecally to wild-type and SOD1G93A 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 that less phrenic motor neurons were dead. Enhanced pLTF in SOD1G93A rats was blocked by siBDNF (13±4%; p<0.05; n=5) but attenuated by siTrkB (74±19; p<0.05; n=5) and non-target siRNA (55±11%; p<0.05; n=5) delivery compared to enhanced pLTF seen previously in SOD1G93A rats (106±24%). Non-target siRNA and siTrkB effects on pLTF were not different from one another (p>0.05), suggesting that attenuation of pLTF in SOD1G93A rats via siTrkB is a non-target effect. Phrenic motor neuron survival in SOD1G93A rats was significantly decreased compared to age-matched wild-type littermates in all treatment groups (p<0.001). In conclusion, enhanced pLTF in SOD1G93A rats is BDNF dependent and plasticity is exhibited by surviving phrenic motor neurons and is not due to a drift in the ALS genetic rat model that would result in decreased phrenic motor neuron death.