Abstract

Amyotrophic lateral sclerosis (ALS) is a degenerative neuromuscular disease of unknown etiology in which upper and lower motor neurons are progressively destroyed. Recent evidences support a role of autoimmune mechanisms in the pathogenesis of ALS. This study investigates the effects of sera from ALS patients on neuromuscular transmission in phrenic nerve-hemidiaphragm preparations and in calcium currents of single dorsal root ganglion (DRG) cells in mice. Mice were injected with either control sera from healthy adults or ALS sera from 18 patients with the sporadic form of ALS, for a period of 3 days. Miniature end plate potential (MEPP) and nerve stimulation-evoked end plate potential (EPP) were measured using a conventional intracellular recording technique and quantal content was determined. Single isolated DRG cells were voltage-clamped, and membrane currents with the whole-cell configuration of patch clamp technique were recorded.

The results were as follows:

1. Sera from 14 of 18 ALS patients caused a significant increase in MEPP frequency in normal Ringer's solution. Mean MEPP frequency in the ALS group (4.62 ± 0.14 Hz) was significantly higher than in the control group (2.18 ± 0.15 Hz, p<0.001).

2. In a high Mg²⁺/low Ca²⁺ solution, sera from 13 of 18 ALS patients caused a significant increase in MEPP frequency. Mean MEPP frequency in the ALS group (6.09 ± 0.38 Hz) was significantly higher than in the control group (2.18 ± 0.31 Hz, p<0.001). Sera from 11 of 18 patients produced a significant increase in neurally-evoked EPP amplitude. The seven remaining ALS sera did not alter EPP amplitude.

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Average EPP amplitude in the ALS group was 1.30±0.04 mV, which was significantly higher than in the control group (0.92±0.05 mV, p<0.001). In the ALS group, EPP quantal content (m) determined by the direct method also tended to be elevated; significant rises were caused by the sera of 14 patients. Mean quantal content in these ALS group mice was 2.35±0.07, significantly higher than in the control group (1.49±0.07).

3. MEPP frequency and amplitude in wobbler mouse was 4.03±0.53 Hz and 1.37±0.18 mV, respectively, the values were significantly higher than those of wobbler controls (wobblers without the symptoms of wobbler).

4. Sera from ALS patients reduced HVA calcium currents in DRG cells. Peak values in control and ALS groups were -2131±160 pA and -911±49 pA, respectively, at -10 mV test potential. ALS sera significantly reduced peak I_{Ca} (p<0.001). There was no significant change, however, in the reversal potential for I_{Ca}, and the I-V curve did not shift. The inactivation curve shifted to more negative potentials in the ALS group. ALS sera changed half-inactivation potential (ALS: -36.76 mV, control: -43.74 mV, p<0.05).

From there results it was concluded that: 1) The serum factor of sporadic ALS patients increases neuromuscular transmission and can alter motor nerve terminal presynaptic function. This suggest that ALS serum factor may play an important role in the early stage of ALS. 2) Calcium currents in DRG cells were reduced and rapidly inactivated by ALS sera, suggesting that in these cells, sporadic ALS serum factor may exert interaction with the calcium channel.

Keywords: amyotrophic lateral sclerosis, neuromuscular junction, quantal
content, evoked transmitter release, calcium channels, dorsal root ganglion, wobbler mouse.