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Synaptic stripping and MHC class I expression in the facial motor nucleus of ALS mice

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Pathogenetic mechanisms involved in the fatal, still incurable neurodegenerative disease amyotrophic lateral sclerosis (ALS), characterized by progressive motoneuron death, await full clarification, important for the development of new therapeutic approaches. In the ALS murine model provided by mutant SOD1(G93A) mice, we here investigated the presynaptic wiring of facial motoneurons in basal conditions and after facial nerve transection (a classical paradigm to examine the retrograde motoneuron response to injury), and major histocompatibility (MHC) class I antigen expression after axotomy. The study was based on fluorescent retrograde labeling of motoneurons, synaptophysin and MHC class I antigen immunostaining, electron microscopy. A significant decrease of excitatory axosomatic boutons was found in presymptomatic ALS mice compared to the wild-type (Wt) counterpart, indicating the occurrence of excitatory synapse detachment (presynaptic stripping) in mutant motoneurons. Synaptic stripping, which seems to represent a protective mechanism preserving the inhibitory input, became more marked in facial motoneurons of symptomatic ALS mice. After axotomy, synaptic stripping was consistently enhanced in ALS mice. In the axotomized facial motoneurons of Wt mice synaptic stripping was accompanied by induction of MHC class I antigens, immune molecules implicated in activity-dependent changes in synaptic connectivity and regeneration after injury. MHC class I antigen induction was instead decreased in the axotomized facial nucleus of presymptomatic ALS mice, and was very low, occurring only in glial cells, in symptomatic ALS mice. The findings demonstrate enhanced loss of excitatory presynaptic terminals, as well as a dissociation between this process and MHC class I antigen expression after injury, in motoneurons which carry a mutation committing them to death. The findings also implicate MHC class I antigen induction in glial cells surrounding ALS motoneurons in this intercellular crosstalk.

Keywords

Synaptic plasticity, neurodegeneration, motoneurons, amyotrophic lateral sclerosis, neural-immune interactions, major histocompatibility complex antigens