

A Muscle Perspective on the Pathophysiology of Amyotrophic Lateral Sclerosis

-Differences between extraocular and limb muscles

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för
avläggande av filosofie/medicine doktorexamen framläggs till offentligt
försvar i Sal KB3B1 (149), KBC-huset,
Onsdagen den 8 juni, kl. 09:00.
Avhandlingen kommer att försvaras på engelska

Fakultetsopponent: Professor Fawzi Kadi,
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Department of Integrative Medical Biology, Anatomy
Department of Clinical Sciences, Ophthalmology
Umeå University, Umeå 2016

Organization
Umeå University
Integrative Medical Biology, Anatomy
Clinical Sciences, Ophthalmology

Document type
Doctoral thesis

Date of publication
June 8, 2016

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Abstract

Amyotrophic lateral sclerosis (ALS) is a late-onset progressive neurodegenerative disorder. ALS has been traditionally believed to be primarily a motor neuron disease. However, accumulating data indicate that loss of contact between the axons and the muscle fibres occurs early; long before the death of motor neurons and that muscle fibres may initiate motor neuron degeneration. Thus, the view of ALS is changing focus from motor neurons alone to also include the muscle fibres and the neuromuscular junctions (NMJs). While skeletal muscles are affected in ALS, oculomotor disturbances are not dominant features of this disease and extraocular muscles (EOMs) are far less affected than limb muscles. Why oculomotor neurons and EOMs are capable to be more resistant in the pathogenetic process of ALS is still unknown. The overall goal of this thesis is to explore the pathophysiology of ALS from a muscle perspective and in particular study the expression and distribution of key neurotrophic factors (NTFs) and Wnt proteins in EOMs and limb muscles from ALS donors and from SOD1^{G93A} transgenic mice. Comparisons were made with age-matched controls to distinguish between changes related to ALS and to ageing. Brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4) were present in EOMs and limb muscles at both mRNA and protein levels in control mice. The mRNA levels of BDNF, NT-3 and NT-4 were significantly lower in EOMs than in limb muscles of early and/or late control mice, indicating an intrinsic difference in NTFs expression between EOMs and limb muscles. qRT-PCR analysis showed significantly upregulated mRNA levels of NT-3 and GDNF in EOMs but significantly downregulated mRNA levels of NT-4 in limb muscles from SOD1^{G93A} transgenic mice at early stage. The NTFs were detected immunohistochemically in NMJs, nerve axons and muscle fibres. The expression of BDNF, GDNF and NT-4 on NMJs of limb muscles, but not of EOMs, was significantly decreased in terminal stage ALS animals as compared to the limb muscles of the age-matched controls. In contrast, NTFs expression in intramuscular nerve axons did not present significant changes in either muscle group of early or late ALS mice. NTFs, especially BDNF and NT-4 were upregulated in some small-sized muscle fibres in limb muscles of late stage ALS mice. All the four Wnt isoforms, Wnt1, Wnt3a, Wnt5a and Wnt7a were detected in most axon profiles in all human EOMs with ALS, whereas significantly fewer axon profiles were positive in the human limb muscles except for Wnt5a. Similar differential patterns were found in myofibres, except for Wnt7a, where its expression was elevated within sarcolemma of limb muscle fibres. β -catenin, a marker of the canonical Wnt pathway was activated in a subset of myofibres in the EOMs and limb muscle in all ALS patients. In the SOD1^{G93A} mouse, all four Wnt isoforms were significantly decreased in the NMJs at the terminal stage compared to age matched controls. There were clear differences in NTF and Wnt expression patterns between EOM and limb muscle, suggesting that they may play a role in the distinct susceptibility of these two muscle groups to ALS. In particular, the early upregulation of GDNF and NT-3 in the EOMs might play a role in the preservation of the EOMs in ALS. Further studies are needed to determine whether these proteins and the pathways they control may have a future potential as protecting agents for other muscles.

Key words: Neuromuscular junctions, Extraocular muscles, Skeletal muscle, Neurotrophic factor, Wnt, Motor neuron disease, Amyotrophic lateral sclerosis, SOD1^{G93A} mice.

Language
English

ISBN
978-91-7601-445-5

ISSN
0346-6612

Number of pages
92+ 3 papers