NEUROMUSCULAR DISEASE

Protecting the nerve terminals

Maintaining the connections between nerve cells and muscle could help to slow the progression of amyotrophic lateral sclerosis.

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It is generally accepted in neurobiology that the integrity of the axon – the cable-like extensions that transmit information between neurons, muscles and sensory receptors – is wholly dependent on the health of the neuron cell body. This concept has been a guiding principle in the search for experimental therapeutics to treat neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis. In this approach, protecting the cell body of the neuron should help to slow down or even stop the progression of neurodegeneration.

However, growing evidence from experiments in animals and observations in humans has shown that neurons, axons, and even the nerve terminals (which connect to the target muscle) respond differently to damage. This suggests that independent mechanisms of neurodegeneration may be at play in different regions of the neuron (Conforti et al., 2007, 2014). Therefore, treatments may need to target the entire neuron to achieve a significant therapeutic impact.

Amyotrophic lateral sclerosis (ALS) is a devastating motor neuron disease that strikes without warning, typically in the prime of life. People with ALS become progressively weaker, which ruthless leads to disability, loss of independence and ultimately death. Therapeutic interventions are largely palliative, and dozens of clinical trials over the past three decades have failed to identify treatments that can slow down – never mind reverse or stop – the progression of this disease.

Promising results from pre-clinical experiments in animal models of the disease have not been successfully translated to humans, and the reasons for these failures are hotly debated. Of particular interest, largely because the findings are paradoxical, have been interventions in animal models of ALS that demonstrated near complete protection of the cell bodies of motor neurons, but failed to slow the progression of the disease. In these cases, protection of the motor neuron cell body by a variety of techniques did not prevent the loss of connectivity between the nerve terminals and the muscle (Gould et al., 2006; Parone et al., 2013; Klivenyi et al., 1999; Suzuki et al., 2007). This loss of connectivity is known as denervation.

Experimental studies in animal models of ALS have shown that the degenerative process of the disease starts at the nerve terminals and progresses proximally to the axon and eventually to the cell body of the neuron, a pattern described as ‘dying-back’ (Frey et al., 2000; Fischer et al., 2004). As with any ‘electrical’ system, the separation of the wire (the axon) from its target (the muscle) results in loss of function – or in the case of ALS, weakness and death. Now, in eLife, Steven Burden and colleagues from NYU Medical School and Columbia University – including Sarah Cantor as first author – report that protecting the connection between nerve and muscle could slow down the progress of the disease (Cantor et al., 2018).
The motor neuron connects to the muscles at
the so called neuromuscular junction, through
which the neuron transmits signals to activate
muscle contraction (Figure 1). Many proteins
help to maintain this connection, including one
called MuSK (Burden et al., 2013). During
development, MuSK stimulates the attachment
of the nerve terminal to the muscle. Later in life,
MuSK is necessary to stabilize and maintain the
neuromuscular junction, which ensures that sig-
nals can travel between the muscle, the nerve
terminal and the motor axon. Indeed,
damage or mutations to the MuSK gene are
linked to other neuromuscular diseases.

Cantor et al. used a well-characterized mouse
model of ALS to test if intervening with already
damaged neuromuscular junctions could slow
the progression of the disease. Their approach
involved using an antibody that binds to and
stimulates the activation of MuSK. The results
showed that with the antibody, the neuromuscu-
lar junctions remained intact and functional for
an extended period. In addition, the death of
motor neurons was delayed, indicating that
maintenance of muscle innervation plays a role
in the support of the motor neuron cell body.

But even so, the animals only survived several
days longer than normally. This might be due to
the aggressive nature of the disease in this ani-
mal model, or possibly due to the lack of
therapeutic targeting of the motor neuron cell
bodies. Nevertheless, these findings suggest
that protection of the neuromuscular junction
could be a way to slow disease progression and
keep neurons alive.

The pathogenesis and progression of ALS is
an enigmatic and vexingly unresolved neurobio-
logical problem. Genes and cellular pathways
that represent possible upstream drivers of the
disease are being discovered on a regular basis,
and all of these may be specifically targeted.
However, the approach of protecting neuromus-
cular junctions by targeting the underlying biol-
ogy of maintenance is agnostic to these
upstream mechanisms and is also not specific to ALS. It could therefore help to preserve function in a variety of neuromuscular diseases where denervation is a major pathological feature.

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References


