Trial offers hope of a treatment for spinal muscular atrophy

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A research team led by the University of Oxford has found a promising treatment for degenerative disease spinal muscular atrophy (SMA), a leading genetic cause of child death.

SMA occurs when people lack a gene called survival motor neuron 1

(SMN1). It can affect children in the womb or adults. This makes them unable to produce enough SMN protein, resulting is motor neurone degeneration and increasing muscle weakness. However, people have an almost identical gene called SMN2.

Existing proposed treatments are based on altering SMN2 to include a crucial part that is found in SMN1, enabling the production of SMN protein. This uses a splice-switching oligonucleotide or SSO. However, the difficulties of getting SSOs across the blood-brain barrier and into the central nervous system mean that they have to be injected into the spine with a lumbar puncture.

Researcher Dr Suzan Hammond explained: 'Intrathecal delivery – injection around the spinal cord – makes a treatment less straightforward. Around a third of patients experience side effects. An additional complication is that SMA frequently leads to scoliosis – twisting of the spine – which can restrict such injections.'

The team at Oxford's Department of Physiology, Anatomy and Genetics developed a treatment called Pip6a-PMO, in which the SSO was delivered using a peptide called Pip6a.

Dr Hammond explained: 'Pip6a is highly effective at delivering SSOs to a wide variety of tissue in the body. We have confirmed that it can also get them into the brain and spinal cords in young and adult mice.'

When young mice – known as pups – with genetically engineered SMA were injected with the Pip6a-PMO, the results were rapidly clear: At just seven days old they were noticeably heavier and faster growing than untreated pups; at 12 days, tests found the treated pups much stronger than untreated counterparts. They also lived much longer, a median 167 days for mice treated with one dose of 10 microgrammes per gram of weight of Pip6a-PMO, compared to untreated pups' 12 days.

Tests also found that two such doses of Pip6a-PMO markedly improved survival – with all mice treated in this way surviving at least 200 days and median survival of 457 days, 38 times longer than untreated mice and nearly three times longer than those who received a single dose.

Study of neuromuscular junctions, where motor neurones connect to muscles, showed that the effect of SMA, which destroys nerves at the junctions, was reversed by a single dose of the treatment, returning the connections to normal levels.

Professor Matthew Wood said: 'While Pip6a was initially designed for Duchenne muscular dystrophy, we have shown that it can also be highly effective in SMA treatment. The survival of mice in this trial was far longer than any other treatment. The advantage is that it is both a central nervous system treatment and a systemic treatment for the wider body. Such an approach could also work for diseases like Parkinson's, Huntingdon's and ALS, and our focus will be extending the clinical applications of Pip-PMOs.'

The team are currently planning a 2-year study that would start next year, to evaluate this treatment in patients.

More information: Suzan M. Hammond et al. Systemic peptide-mediated oligonucleotide therapy improves long-term survival in spinal muscular atrophy, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1605731113

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