MND AUSTRALIA INTERNATIONAL RESEARCH UPDATE

JUNE 2020

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Pulling together to Defeat Motor Neurone Disease

While the world has come to a standstill, motor neurone disease (MND) has not, and neither have research efforts. Across the globe clinicians, scientists and their teams are working harder than ever to defeat motor neurone disease.

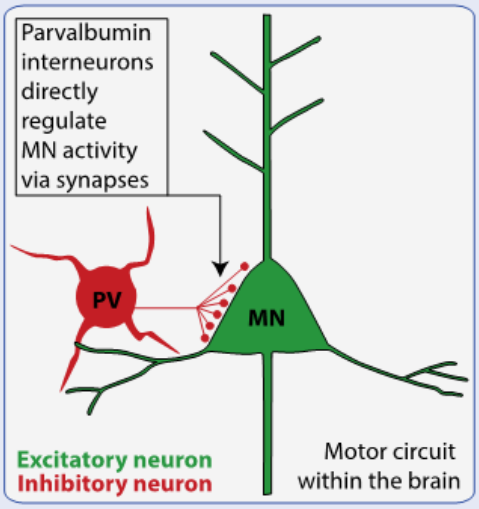
In this issue of the international research update we focus on activity in the brain and how this may affect disease, as well as understanding how the body attempts to restore connections between degenerating neurons and muscles in the disease. We also touch on the new frontier that is the gut microbiome and how this may influence motor neurone disease.

Putting the brakes on hyperactive motor neurons delays disease onset in mice

Targeting the activity of motor neurons in the brain may delay the onset of disease and extend survival, according to a new study published in the March edition of *Brain*.

In a series of elegant experiments, Professor Melanie Woodin and colleagues at the University of Toronto have discovered that correcting an imbalance of motor neuron activity - called hyperexcitability (or too much firing) - in the brain, can significantly slow the onset of symptoms in the *SOD1* MND mouse model by preventing neuronal degeneration. This is quite exciting as hyperexcitability is a common feature of MND.

A balancing act in the brain. Normally, for signals to be sent around the body a balance between excitation and inhibition is required, which can be thought of as 'on' and 'off' signals - or 'accelerate' and 'brake'. If you have too much acceleration your car will become uncontrollable, and if your brakes are on too much, then the car won't go anywhere. For normal brain function, and motor function, this balance between excitation and inhibition is essential. In MND, this balance appears to be lost, and neurons start firing too much – or become hyperexcitable.



Inhibitory cells can reduce excess firing. By targeting a specific cell type in the brain called an interneuron, which controls inhibition, Woodin and colleagues were able to put the brakes on excessive neuronal firing in *SOD1* mice. In an encouraging outcome, corrected inhibition not only delayed symptom onset and slowed disease progression, but also caused some weight gain, alongside extended survival in these mice. Key to their success was the observation of a special type of interneuron that directly synapses onto motor neurons (the parvalbumin-interneuron) had reduced activity in the *SOD1* mice. By boosting the activity of the parvalbumin-interneurons, they could restore adequate inhibition to keep excessive motor neuron activity in check, delaying neuronal degeneration. This may represent an important way forward, particularly as reduced inhibition is a common feature of the brain in people living with MND.

MND Research Shorts

- Normal aging involves the accumulation of DNA damage in our cells, which is kept in check by DNA repair mechanisms. Recently, researchers from the University of Sheffield and Oxford University have discovered a new way to repair these DNA breaks, which have been linked to cancer and an increased risk of MND. Age is a risk factor for most neurodegenerative diseases, as it leads to an accumulation of DNA damage that accelerates the degeneration of neurons. The discovery of this novel 'DNA repair kit' is hoped to lead to new therapeutic avenues for preventing neuronal loss in diseases such as MND.
- Researchers from Québec in Canada may have identified the main genetic cause of early onset juvenile MND, which affects young adults before the age of 25. In 43% of juvenile MND cases, they found mutations in the FUS (fused in sarcoma) gene. In the fastest progressing cases, a mutation in the NLS region of the gene was largely to blame. The NLS signal on FUS usually helps the FUS protein stay within the nucleus of cells but, when mutated, FUS abnormally accumulates in the cytoplasm of motor neurons. Many groups around the world are working on ways to better clear abnormal protein clumps in cells as potential therapeutic approaches for MND and other neurodegenerative conditions.
- Clinicians and medical researchers from the University of Sydney have been using a special imaging technique called transcranial magnetic stimulation (TMS) to take a snap shot of brain activity in people living with MND. By measuring brain activity over time, they were able to identify that cortical hyperexcitability – or excessive neuronal firing – tracked with disease progression, and was linked to the progressive failure of inhibitory circuits, and presumably inhibitory neurons.
- A designer DNA drug therapy, termed "gene therapy", has corrected the genetic cause of spinal muscular atrophy (SMA), an inherited form of childhood MND. This raises hopes for the future development of designer drugs to correct other genetic mutations involved in MND, such as SOD1, FUS, TDP-43 and C9orf72. A number of companies are working on different approaches to directly target patients carrying mutations in these genes and the first examples are currently being trialled for SOD1 (Tofersen) and c9orf72 (BIIB078). Drugs targeting FUS are also being developed, as well as a number of different ways to deliver the drugs to the motor neurons.

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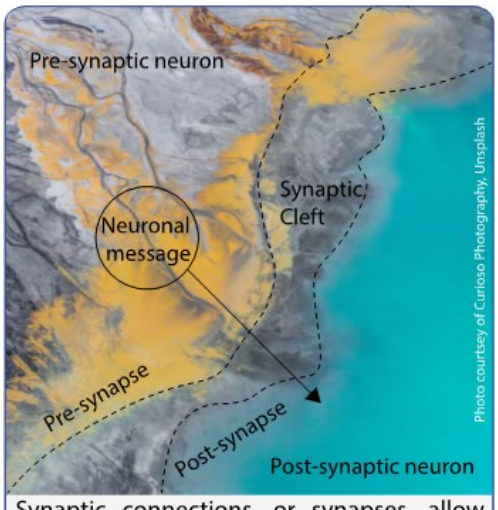
Synaptic repair mechanism may help maintain nerve-muscle connections in MND

Berkeley National Laboratory and the University of California, San Francisco have been trying to understand how the body attempts to protect synapses from degenerating in MND.

What are synapses? The junction where one neuron meets another neuron is termed a synapse. These small, but important structures, are the sites at which neurons communicate information to each other. In the motor system, synapses are vital connection points that allow for the relay of information from the brain through the spinal cord to the muscle. In MND, the synapse comes under fire very early on in disease, resulting in a rift in essential motor communication.



Synaptic connections, or synapses, allow electrical signals to be relayed between neurons. The pre-synaptic neuron relays the message across the synapse to the post-synaptic neuron that receives the message.

Synaptic resilience. Published in the May edition of the journal *Neuron*, the research collaboration demonstrated the presence of a neuroprotective mechanism, which helps maintain the synaptic connection between muscle and motor neurons. It had previously been assumed that a compensatory mechanism might temporarily counteract synaptic deterioration, and delay neurodegeneration, but its nature was unknown. Described as "***Presynaptic homeostatic plasticity***" this powerful self-corrective mechanism allows synapses to remodel and stabilise information transfer at synaptic connections. When this 'homeostatic plasticity' was blocked in a mouse model of MND -like degeneration, it accelerated the loss of motor neurons and disease progression two-fold. Lead author, Briar Orr, Ph.D. suggests this plasticity, if harnessed correctly, could confer resilience at the synapse and act to limit disease progression in MND.

Gut microbes linked to survival in C9orf72 disease

Billions of bacteria and microorganisms in our gut help us to digest food. In fact, we carry up to 2 kg of microbes in our digestive system, and some of these are quite unique to us as individuals - making up our "microbiome". As we learn more about this dynamic ecosystem within the gastrointestinal system, it should come as no surprise that these gut microbes may contribute more to our health than we previously realised.

A new study, published in the journal *Nature*, has found evidence that the gut microbiome may influence inflammation and survival in a genetic model of MND. Led by Professor Kevin Eggan, researchers from Harvard University had been attempting to learn more about the most common genetic cause of MND, *C9orf72*. However, the team hit a snag when they found that genetically identical mice had varied disease characteristics, survival and disease progression. Puzzled by this phenomenon, they began to look for biological factors that might explain these differences.

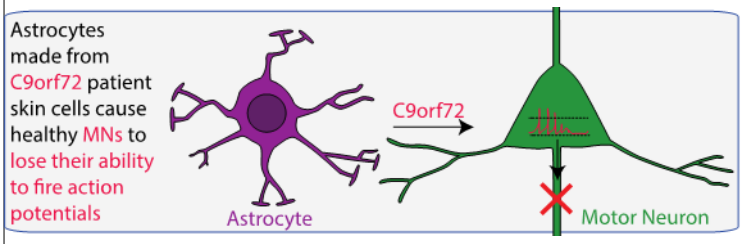
Surprisingly, answers were found in the gut microbiome. Not only did the mice have different species of microorganisms in their gastrointestinal system, but the species of microbes seemed to modify the severity of inflammation in the *C9orf72*-deficient mice, and their survival. While it remains unclear if each pathogenic MND mutation has a unique relationship with gut microorganisms, this study illustrates that gut microbes can influence the severity of inflammation caused by C9orf72-deficiency. To learn more about this connection, the researchers are planning to examine the link between inflammation and the microbiome of people with MND.

Support cells expressing C9orf72 damage motor neurons

Astrocytes reprogrammed from MND patient cells can directly cause healthy motor neurons to stop producing the electrical signals they need to control muscle, according to new research from the journal *Glia*.

What are astrocytes? These star-shaped cells in the brain and spinal cord have multiple support roles in the central nervous system, including helping to supply the energy necessary for neurons, the brain cells within the nervous system, to communicate and store information.

Researchers from the University of Edinburgh, University of St Andrews and King's College London have been working together to investigate how astrocytes contribute to motor neuron vulnerability. Led by Professor Gareth Miles and Professor Siddharthan Chandran, the team used stem cell technology to firstly reprogram cells from *C9orf72* patients' skin samples into astrocytes and motor neurons (using induced pluripotent stem cells (iPSCs)).



Remarkably, by growing the *C9orf72* astrocytes in a dish with motor neurons, they not only showed that *C9orf72* motor neurons became dysfunctional, but control motor neurons that should have been healthy, also began to lose their ability to work properly.

This suggests astrocytes are central to MND, as they can directly cause motor neurons to stop functioning, even before they show signs of degeneration. The authors hope this discovery leads to the development of much-needed MND treatments and, ultimately, a cure.

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The *MND Australia International Research Update* is generously supported by MND Victoria