MND Australia Research Update

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As of 2012, I have taken over the role of reporting quarterly on the latest research discoveries in motor neurone disease (MND). I have enjoyed reading Dr Justin Yerbury's updates over the last few years and reflecting upon this, with his ability to succinctly break down scientific jargon into something that everyone can understand, I realise I have rather large shoes to fill!

So who am I? I am one of the 2011 Bill Gole Postdoctoral Research Fellows supported by MNDRIA, based at the Menzies Research Institute of Tasmania. Their support has enabled me to investigate why neurones stop functioning in MND, and the role over excitation of neurones plays in neuronal dysfunction. Research into MND is constantly evolving and investigators are steadily working towards uncovering aspects of the disease that may be therapeutically targeted to reduce the devastating consequences. Through the MND Australia Research Updates I will endeavour to keep you up to date with newly emerging studies in this complex field of research.

If you have ever been stuck in London's underground in peak hour when a train breaks down, you will truly understand the chaos that a disruption in transport can cause. Like the commercial heart of the city, neurones live and die by the efficiency of their transport systems.

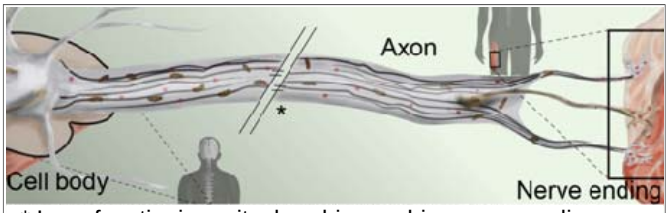
Recent research makes it clear that disruption in active transport in motor neurones can have very serious consequences, particularly when the disruption affects mitochondria. This research update will focus on the latest research into the transport and function of mitochondria in motor neurone disease.

Mitochondria transport in MND

A range of genetic mutations have been identified in the inheritable forms of motor neurone disease, and during January two interesting papers were published investigating how some of these mutations affect the transport of mitochondria.

Giovanni Manfredi's New York based research group investigated the dynamics of mitochondria in motor neurones that carry the superoxide dismutase 1 (SOD1) mutation, and showed that there were less mitochondria on the move, and furthermore the mitochondria that had been successfully transported were making less energy. In another study, Gabor Morotz and colleagues in London showed that a different MND mutation affects interactions between the transport machinery and the microtubule tracks.

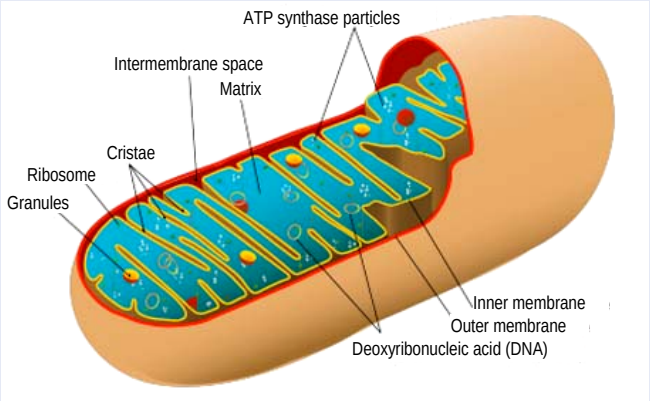
These two papers suggest that mitochondria transport disruption may be a common theme in motor neurone disease, implying that fewer, or less functionally adequate mitochondria are reaching the far outskirts of nerve endings in patients with MND. If mitochondria aren't transported, or arrive in a dysfunctional state, the neurone does not get the energy it needs to work.



* Less functioning mitochondria reaching nerve endings = less energy for the neurone

What are mitochondria?

Mitochondria are the power plants of a cell. They combine the sugars we eat with oxygen to produce an energy source (ATP) that is useable for the cell. Neurones have a high energy demand and so their mitochondria are very important to them. Mitochondria are continuously transported on 'train tracks' (microtubules) around neurones and down the axon to the nerve endings – wherever energy is required.



How do we investigate the transport of mitochondria?

Technological advances over the last few decades have enabled researchers to see mitochondria moving within the neurone in real time. Mitochondria can now be 'tagged' with a fluorescent marker, and using state of the art microscopes, the movement of the coloured mitochondria can be investigated.

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The buzz on chromosome 9.

Researchers all around the world are excited about the discovery of the C9ORF72 mutation, highlighted in the December edition of the MND Australia International Research Update. Indeed, no less than nine papers investigating this short repeated sequence were included in the most recent edition of *Brain*. Many of these studies focus upon the links between motor neurone disease and dementia. This association is important since it may help scientists to better understand what is happening in the brain, but equally importantly it will help doctors better understand the symptoms of their patients.

Setting the stage for MND.

Also in the March edition of *Brain*, scientists in the UK have proposed a simple staging system for motor neurone disease, where each stage is clearly identified based upon the severity of disease. By analysing 1471 patients with MND, Jose Roche and colleagues identified the important stages in the disease progression, starting from symptom onset. Staging criteria for MND will help patients, care givers, doctors and scientists by providing a simple and objective measure of disease progression, allowing more precise comparisons of treatment effects as well as clearer disease prognosis.

Are neurones and muscles complaining too much?

Researchers at the University of California, San Francisco have made an important discovery in the fruit fly. Investigating motor neurones, which selectively die in motor neurone disease, Keller and others proved that when motor neurones becomes sick they communicate with their surrounding cells, which in turn signal back to the neurone, increasing the strength of the distress signal. Understanding this communication may be an important avenue of investigation to working out how to stop the spread of disease in MND.

Sunshine, too much of a good thing or not enough?

Jesse Solomon and colleagues in Toronto, Canada have shown that vitamin D levels may be important in MND. Our bodies produce vitamin D in the presence of sunlight, and it has been shown to increase motor neurone survival and now also to increase performance on motor tests in mice with a similar SOD1 mutation to some cases of human MND. However the study is not as simple as it may seem: they also found that vitamin D deficiency delayed disease onset. Hence the effects of vitamin D supplementation remain uncertain – perhaps requirements differ at different stages of the disease?

Turning MND off?

There are strong links between mutations in the DNA editing proteins and MND. Pennsylvania, USA based scientists Cao Huang and colleagues have created new transgenic rats in which the expression of one of these mutations (TDP-43) can be turned on and off specifically in motor neurones and skeletal muscle. They found that turning on this mutant protein in motor neurones alone was enough of an insult to cause significant motor neurone death and paralysis in the rats. However, it was what happened after it was turned off that was most exciting. Stopping the disease gene prevented the paralysis from getting worse. Furthermore they found that if there was only a limited loss of motor neurones then dramatic recovery of motor function occurred. This could mean that the progression of the disease could possibly be halted in MND patients if the diagnosis is early enough, providing we find an effective treatment to do so.

Energy balancing act?

MND patients sometimes have higher energy expenditure than normal even when they're not moving. This energy expenditure cannot be accounted for by any of the clinical symptoms of the disease. Lim and colleagues in Philadelphia, Pennsylvania introduced mutant SOD1 in a worm model to show that this higher resting energy expenditure may be due to specific abnormalities in how energy production is controlled. Additionally they found that genetically correcting for this imbalance improved the mobility of SOD1 worms.

MND Research Shorts

- Researchers in Japan have reported on a new model of MND in monkeys. These monkeys developed some markers of disease that are present in humans, and may offer a new model to help us study the disease.
- Also in Japan, researchers report on another new mouse model that can be used to monitor oxidative stress levels following different stimuli. Oxidative stress is a toxic cellular process that has been proposed as an explanation for cell death in MND, specifically because mutant SOD1 increases oxidative stress levels. Therefore this mouse model may be useful for investigating oxidative stress levels in MND.
- High levels of proteins produced from the breakdown of oxygen can make neurones sick (oxidative stress). Researchers in New York, USA have discovered a new way in which these by products are produced.
- Canadian based researchers in Quebec have been investigating the effects of mutations in the TDP-43 and FUS genes on the ageing of neurones. They report that mutant TDP-43 and FUS have a greater effect on neurone death as the neurones get older in the worm model.

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