MND Australia
International Research Update

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Disappointing result from dexpramipexole trial

Over the last decade Biogen Idec has been trialling a new drug to treat motor neurone disease. Researchers have shown that a variety of factors may contribute to MND. One such factor is that the power plants of the cell, the mitochondria, stop working as well as they should. Without enough energy a cell can become sick very quickly. Dexpramipexole, the drug that Biogen was trialling, acted on strengthening the mitochondria. Early clinical trials showed that the drug slowed the disease's progression in some patients involved in the study. This gave hope that while it might not be the right drug for everyone with MND, it might at least help a subset of patients in future trails. However the last, larger phase of clinical trails failed to repeat these results, with dexpramipexole failing to improve the survival or quality of life of late stage patients. This is disappointing for everyone involved in the MND communities as there has not been a drug approved for motor neurone disease for 15 years and dexpramipexole did indeed appear promising.

The disappointing results of this recent clinical trial highlight the difficulty in developing new treatments for MND. The underlying cause of MND remains unclear so it is important for the global research community to keep working at unraveling all the factors that lead to MND in order to devise better treatment strategies.

Biogen has stated that they will continue working towards development of new treatments for motor neurone disease.

Why target mitochondria?

Mitochondria are the power plants of cells; they produce the energy the cell needs to function. They do this by converting the sugar we eat into an energy source the cell can use, known as ATP. Without enough available energy a cell can become sick very quickly. Motor neurones are very specialised cells with a very high-energy demand. This means that they are very reliant on their mitochondria to work properly. There is convincing scientific evidence that mitochondria stop working properly in motor neurone disease. This would result in the motor neurones not getting enough energy and so they degenerate. Therefore to treat motor neurone disease one key step will be making sure the mitochondria are functioning normally.

What do elite athletes and MND have in common?

National Football League (NFL) players are four times more likely to develop MND during their life, new research has shown. The question of whether there is a link between MND and playing professional football has been around for a long time. In America the most common form of MND is known as Lou Gehrig's disease, named after the famous baseball player who had a long and successful career that abruptly ended when he was diagnosed with MND. Evidence between elite athletes and MND was found more recently in Italy where numerous studies have shown a greater risk for professional soccer players to develop MND. These studies also suggest that the risk of developing MND gets greater the longer the professional athletes play. There have been many proposals about the reason for this increase of MND in elite sportsmen, but no clear-cut evidence has been found.

The rate of MND in elite athletes has now been addressed in the National Football League in America. Everatte Lehman and colleagues at the National Institute for Occupational Safety and Health, Ohio, USA conducted a study on 3,439 footballers who played for at least five years in the NFL between 1959 and 1988. They found that when compared to the general population these players were half as likely to die during the period they investigated, which is not surprising as these men would be in top physical condition and have easy access to medical advice. However, the NFL players were at least three times more likely to die of a neurodegenerative disease. Further analysis of the NFL data revealed a fourfold increase in the percentage of MND and Alzheimer's disease cases, with MND having the greatest increase compared to the general population. Player position of the footballers was then classified into two categories: speed (linebackers, running backs, and quarterbacks) and non-speed (defensive and offensive linemen). The speed players had nearly a sixfold greater risk of developing a neurodegenerative disease while the risk for non-speed players was only one-and-a-half times greater than that of the general population. The speed players are the ones who have a greater speed when they tackle and therefore have a greater number of concussions. This suggests that there may be a link between trauma to the head and body and MND.

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Growing motor neurones to be healthy and strong

Researchers from the University of Würzburg, Germany have discovered how ciliary neurotrophic factor (CNTF) can protect neurones in motor neurone disease. CNTF is a protein produced from cells that support nerves and nerve endings and help them function well. A few decades ago CNTF was shown to improve survival in a mouse model of MND, however the specific way the growth factor was acting on motor neurones to increase their survival was not known. The Sendtner laboratory at the University of Würzburg recently published their work in the *Journal of Cell Biology* demonstrating that this growth factor works by fixing the internal scaffolding of the neurone, the cytoskeleton. Scientists have been interested in this growth factor as a treatment for MND for a long time, and it has even been taken to the clinical trial stage to see if it can improve patients with MND. However the patients treated with CNTF developed some bad side effects and the trial was stopped. It was believed that the side effects were due mostly to too much of the growth factor ending up in the liver and not enough in the nervous system. The recent work sheds light on how the growth factor actually works. This knowledge will be important because now they know the site of action they might be able to work out a more targeted way of delivering the growth factor. This means there is still hope for CNTF to be used as a therapeutic because if less of the drug is needed then, hopefully, the build up of excess growth factor in the liver could be avoided.

Are neurones not talking enough?

There are two main type of neurones in the nervous system, the excitatory neurones, which are the neurones that fire and send a signal or cause a muscle to contract, and inhibitory neurones which modulate the firing of excitatory neurones. These two types of neurones work together to form the circuit of the nervous system. MND is caused by the dysfunction and ultimate death of a certain type of excitatory neurone, the motor neurones. Research just published in the *Journal of Comparatory Neurology* has highlighted an important role for the inhibitory neurones in the dysfunction of these motor neurones. Hanna Wootz and colleagues at Uppsala University, Sweden have shown that a disruption in the inhibitory control of motor neurones occurs early in a mouse model of the disease and could contribute to the reason why motor neurones stop working properly.

Best thing since sliced bread

Maria Armakola and colleagues at Stanford University, California have uncovered a new player in the form of MND caused by mutations in the RNA binding protein *TDP43*.

Using a genetic screen in yeast cells these researchers showed that stopping a gene called *Drb1* from working decreases the ability of mutated *TDP43* to be toxic. Mutated *TDP43* forms sticky clumps of protein known as aggregates inside motor neurones and these aggregates have toxic effects. Knocking out the *Drb1* gene in yeast cells moved these sticky aggregates away from the RNAs that are needed to make protein inside the cells and hence stopped these aggregates from having their toxic effects. Furthermore they also showed that the *Drb1* gene has the same effect in rat cell lines and neurones cultured in a dish. Stopping the *Drb1* gene from working in patients with MND could be a new therapeutic way to tackle this devastating disease.

Two diseases sharing the same genes

Manal Farg in Julia Atkin's laboratory at Latrobe University Victoria has found a potent modifier of a gene that is know to cause some of the inherited forms of MND. This gene is called the fused in sarcoma (*FUS*) gene which, like *TDP43*, is involved in the reading and translation of RNA and DNA. Scientists at Latrobe University showed that in human cases of MND where they found mutated *FUS* protein, they also found another gene product called *Ataxin 2*. They found that if they induced neurones in a dish to produce both gene mutations at the one time, the neurones became very sick. *Ataxin* is a gene that, when faulty, causes a disease in the central nervous system known as spinocerebellar ataxia. This slowly progressive disease causes people to have difficulties with their movements and coordination. This gene may also play a role in MND and could be a new therapeutic target to investigate in the fight against motor neurone disease.

MND research shorts

- *Researchers in Belgium have shown that deleting an enzyme that is involved in controlling axonal transport slowed disease progression in the MND mouse model.*
- *Again in Belgium, researchers have shown that human stem cells can survive in a rat model of MND, giving hope that stem cells might be a potential therapy to treat motor neurone disease.*
- *Using state of the art cell culture techniques researchers in New York have revealed that neurones and non-neuronal cells derived from a mouse model of motor neurone disease closely interact with each other and affect the gene expression of other cells.*
- *Researchers in Japan have shown that decreasing the levels of DNC-1, the protein responsible for the transport of the neurone's garbage, leads to motor neurone dysfunction and death, further highlighting the important role this protein may play in motor neurone disease.*

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