The potential for retrotransposon mobilisation to modulate sensory loss in ageing

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Introduction

The statement ‘ageing is a major risk factor for many neurological disorders’ is often overlooked as scientists and clinicians rush to explain specific mechanisms underpinning the initiation or progression of these disorders. However in the main, diseases like Alzheimer’s, Parkinson’s and Motor Neuron Disease are clearly associated with ageing, although unfortunately young people can also suffer from these conditions. It is also fortunately not true, that these diseases are an unavoidable consequence of ageing. The same can be said of age related pain, in that there is much debate on whether chronic pain is experienced more by older people, e.g. the elderly often experience chronic pain in the joints but less visceral pain and headache.

Our study will expand upon the following observation ‘as we age, we have increased mutation of the DNA in the brain’ to address if a similar mechanism is observed in more peripheral neurons associated with transmission of pain to the brain-the sensory ganglia such as dorsal root ganglia. Increasing mutation in these neurons with age would cause these sensory neurons associated with pain transmission to behaviour aberrantly e.g. constantly transmitting a pain signal to the brain or transmitting a pain signal to what otherwise would be considered a low threshold of pain insult.

Our neurons, in the main, are ones that you are born with so once a mutation occurs you have it for the rest of your life. The type of mutation on which we are focused only occurs in neurons in normal tissues and is proposed to increase in frequency with age. The media has termed this class of mutation the ‘jumping gene’ and they are termed ‘retrotransposons’ in the scientific literature. These jumping genes are able to make copies of themselves and these copies reinsert into the DNA of a neuron in a new location hence the term ‘jumping’ and this will in some cases result in changing the function of the neuron. So in short, as we do not replace our neurons the rate of jumping multiplied by our age will increase our likelihood of these jumping genes causing cell damage. To date this effect has only been observed in the brain, therefore if we can prove this ‘jumping’ phenomenon happens in the more peripheral sensory ganglia it opens up a whole new mechanism that is so far not being addressed in pain studies.

We are also studying this DNA jumping mechanism in neurodegenerative conditions. In a recent research study it was suggested that motor neurone disease was caused by a tsunami of these jumping retrotransposons in the brain, this obviously attracted a lot of media attention. However this jumping happens in neurons in the brain in

people without any neurological disease and is an accepted part of growing old, indeed it happens in many species. Perhaps CNS disease is just an unfortunate consequence of the lottery of where the jumping gene reinserts to cause the most damage. In relation to pain, our model would be that with both normal levels of jumping or increased jumping in response to a trauma, the sensory neurons would become less fit for purpose and the normal pain signals become compromised. This compromised control of pain pathways would result in a large variation of pain thresholds in the ageing population.

If we can validate this mechanism in pain transmission it will open up a whole new field for therapeutic intervention such as drugs that target the jumping and reinsertion of these jumping genes.

What are we doing to test our hypothesis?

We have the reagents and probes to address the jumping genes from our ongoing studies in neurodegenerative CNS conditions and these will be used to determine whether a similar jumping gene mechanism is operating in more peripheral neurons and the spinal column. We will test this in both human and mouse neurons involved in pain transmission.

For mouse neurons, which are clearly easier to obtain, we are collaborating with colleagues working in pain models at the University of Pecs in Hungary, Professor Helyes. Indeed this is the same group I introduced to Dr Andreas Goebel, Walton Centre, for his work in fibromyalgia. We have already obtained ganglia from their models in Pecs and we are in the process of doing quality control and initial testing for mechanisms related to the jumping genes. We are also going to compare the jumping gene mechanism in aged mouse models.

To obtain human neurons to make our work more rapidly translational we are collaborating with Dr B Frank, Walton Centre. Dr Frank is obtaining appropriate ethical permission for these studies.

The project has been operating for 6 months and our PhD student on this proposal, has worked with the group in Pecs, developed the necessary skills to isolate and grow peripheral ganglia from mouse tissue, and the skill set to perform molecular and cellular biology for analysis of the jumping mechanism and the proteins involved in controlling their jumping. This work is now ongoing in Liverpool. The jumping in the scientific literature is termed ‘mobilisation’ hence the title of proposal. Our experiments are clearly at an early stage but progressing well and we would expect to have initial data on the jumping mechanism in sensory neurons within the 1st year of the proposal as the experiments are going very well.