

Defects in Neuromuscular Transmission May Underlie Motor Dysfunction in Spinal and Bulbar Muscular Atrophy

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The abstract for this paper can be found [here](#) – this also includes a link for the entire paper. FYI, Dr. Jordan is our newest member of the Scientific Review Board of the KDA.

Summary:

This is a very complicated paper in that it deals with electrophysiological experiments that are quite difficult for the layman (and many scientists!) to understand completely. As a result, I will try to explain the general findings and their significance for possible treatments.

A. Background Information:

1. Kennedy's Disease

Kennedy's Disease (KD) is caused by a mutation in the gene that contains the instructions for synthesizing the protein known as the Androgen Receptor (AR). The AR is the protein that mediates all the effects of the male hormone, testosterone (which, along with its cousin, dihydrotestosterone, is the major androgen in humans). For reasons that I will not go into here, the major symptoms of KD only occur in individuals with high levels of androgens (i.e. males).

For most of the past 25 years, it was believed that KD was a disease caused by the death of motor neurons, the cells that control the contraction of muscles. Recently, however, strong evidence has been presented that the muscle cells themselves are directly affected by the mutation. What is not clear, however, is whether the disease symptoms are only due to the effects on muscles or are due to a combination of changes that are occurring in the both nerve cells and the muscles cells. What does appear to be true is that treatments that target only muscles cells have been effective at relieving the symptoms of KD in animal models. This is important because technically, it is much easier to target treatments to muscle cells than nerve cells and that is a good thing for us with KD.

2. Neuromuscular Junction

The neuromuscular junction is the anatomical site where the motor neuron meets the muscle cell. It is through this structure that the motor neuron controls the contraction of the muscle. This is done through the release of a chemical neurotransmitter known as acetylcholine (ACh) into the neuromuscular junction. ACh then binds to a protein known as the acetylcholine receptor (AChR) which triggers contraction of the muscle. While this is a complicated mechanism, for the

purposes of this review, you only need to know that the contraction of the muscle cells also requires the use of another protein that is known as the sodium channel.

B. What did the researchers report?

The crux of the study was an investigation on the release of ACh at the neuromuscular junction in mice models of KD. All mice were selected after the onset of muscle weakness, thus they were symptomatic. The techniques involved are quite technical in nature and I do not feel that there is any need to go over the specific results. So in summary, what they found was that the amount of ACh released and the response by the muscle to that ACh release changed in KD mice as compared to normal control mice, in general, this means that the efficiency of the stimulation of the muscle by the motor neuron is impaired in the KD mice. In addition, the researchers were able to demonstrate that there were changes in the makeup of the AChR and the sodium channel in the KD mice, suggesting that some of the defects at the neuromuscular junction are due to these changes.

C. What does this mean for a KD patient?

This is a difficult question. There is no doubt that this is an important finding with regard to changes that occur in muscles in KD mice and it is a study that I feel was too long in coming. Any information on the progression of the disease could be helpful and may result in a new path for treatment. As I see it, one of the issues with this study is that it is not clear if the changes in the activity of the neuromuscular junction are the cause of the muscle weakness or a result of it. I am not sure that this paper addresses this issue. If the changes are due to the muscle weakness, then it is not clear that treating this would prevent the general symptoms of KD.

My personal feeling is that other treatments that attempt to with decreasing the amount of mutant AR (siRNA, for example) are well on the way and are more likely to produce a significant treatment. Nonetheless, this is an important paper with regard to the natural history of KD.