HOW MUTATIONS IN SYNAPSIN I AND SYNAPSIN II CONTRIBUTE TO SEIZURE-LIKE ACTIVITY AND EPISODES IN INDIVIDUALS WITH EPILEPSY

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ABSTRACT: Epilepsy is one of the most prevalent neurological disorders and has been associated with abnormalities in the functioning of synapse proteins known as synapsins. Here, we aim to further develop our understanding of how mutations in Synapsin I and Synapsin II may be correlated to seizure-like activity and episodes in individuals with epilepsy. In the quest to successfully establish an understanding, the work of three different articles will be synthesized together to provide a comprehensive literature review. Upon examining work done by an array of investigators and experts in this field, we see that mutations in Synapsins I and II, individually or simultaneously, can contribute to the seizure-like activity and episodes that individuals with epilepsy suffer in a chronic manner. This work is of vital importance to further understand how new methods, specifically pharmacological, can be created and devised to cure an epileptic individual's episodes in the future.

Introduction

Epilepsy is one of the most common and widely-researched neurological disorders that we are currently aware of. Furthermore, epilepsy is characterized by seizures that are chronic, and the episodes of this vigorous shaking and inability to control body movement vary greatly in a wide array of different points in times. Potential causes of epilepsy have been pinpointed, but the underlying mechanism of the disorder still remains unclear. One substantial sub-area of research being done within this field is examining how the connections between neurons may be different in individuals who suffer from epilepsy, relative to individuals who don't suffer from the disorder. Neurons are brain cells that connect to each other via synapses, where chemical messengers known as neurotransmitters are released from the first or pre-synaptic neuron onto the second or post-synaptic neuron. This process is vital to a multitude of mammalian functions such as heart and muscle contractions.

In continuation of the theme of how synaptic connections may be suffering from an abnormality of some sort in individuals with epilepsy, it's critical to understand what synapsins are, and the implications they present. Synapsins are proteins that are currently understood to bind to synaptic vesicles that contain the neurotransmitters which are transmitted from one neuron to the next, thus demonstrating that synapsins may play a significant role in neurotransmitter regulation (Lakhan et al, 2010). There are currently three members of the synapsin family that we are currently aware of, those being Synapsin I, Synapsin II, and Synapsin III. An important aspect to take note of is that Synapsin 1 and Synapsin 2 are often written as SYN1 and SYN2 respectively. With the current foundation we have laid down, it seems practical that mutations in synapsins may be creating abnormal neurotransmission, thus resulting in the seizures we see in those with epilepsy. This literature review examines work previously done that was aimed to understand how mutated forms of both SYN1 and SYN2 are potentially correlated with the neurological disorder of epilepsy. Ultimately, the objective is to understand how mutations in the two more-researched and better-understood synapsins, that being SYN1 and SYN2, may be associated with epileptic and seizure-like activity.

Body

To understand whether or not mutations in SYN1 and SYN2 could be correlated with epilepsy, it is of vital importance to examine scenarios in which only one of the two proteins are mutated, then dive into situations where both proteins have been mutated. To understand SYN1 to a greater extent, Garcia et al did extensive work with a four-generation family. This family has some males who suffer from epilepsy alone while other males suffer from a combination of epilepsy along with learning disabilities, macrocephaly, and aggressive behavior (Garcia et al, 2014). To better understand the particular causative factors explaining these neurological deficits in the males of the family, Garcia et al performed linkage analysis, which consisted of extracting DNA, or deoxyribonucleic acid, from the blood, amplifying and priming it, and running gel electrophoresis of those samples. For the linkage analysis, a common linkage program known as MLINK was utilized by the investigators. These steps were crucial to take in order to understand what gene or genes fell in the segment of the X chromosome microsatellite polymorphisms, where they would be deemed as causative. Garcia et al found that SYN1 was present in this region, and upon screening the protein for any potential mutations, the investigators discovered that there was a mutation in the gene that encoded for Synapsin I, thus prompting the conclusion that this mutation is likely the cause of epileptic phenotype seen throughout the generations of this family.

Likewise, Lakhan et al examined individuals in their study, but the sample size was far greater with 571 individuals, 372 of which had epilepsy. The aim of their work was to better understand SYN2's potential role in epileptic activity. The group had hypothesized that an A>G mutation in the rs3773364 polymorphism of the SYN2 gene would be more prevalent in the individuals who suffered from epilepsy (Lakhan et al, 2010). This particular mutation essentially describes that instead of having an "A" in the segment of the gene, like the individual's ancestor had, the individual themselves has a "G" in the very same position instead. The rs3773364 polymorphism refers to the portion of the SYN2 gene that is of specific interest in this study. To test their hypothesis, Lakhan et al isolated DNA samples from each of the subjects, primed them via the polymerase chain reaction and restriction fragment length polymorphism methods, before performing gel electrophoresis and utilizing SPSS (Statistical Package for the Social Sciences) software for the statistical analysis. The group found that the frequency of the A>G mutation was substantially higher in the epileptic subjects relative to the control subjects, although no other particular mutation within the polymorphism was detectable to have a significant difference in its frequency to the same extent (Lakhan et al, 2010).

Aside from mutating either SYN1 or SYN2 at a time, there are benefits in mutating both proteins simultaneously to see if there's still a correlation with epileptic and seizure-like activity present. Fassio et al explored this idea by mutating Synapsin I and II individually and then simultaneously. The group was of the mindset that mutations in the aforementioned proposed synapsin I and II combination would indeed be correlated with an epileptic phenotype (Fassio et al, 2011). To test this idea, the group drew from previous work that has already been done in the field in order to contribute to the development of the understanding of synapsin mutations and epilepsy. Fassio et al created mice lines consisting of mutations of just SYN1, just SYN2, and SYN1 and SYN2 simultaneously, or all three synapsins simultaneously. All neurons of interest were cultured under well-controlled conditions and electrical activity was recorded with electrodes. The key result that arose from the work was that the most intense epileptic activity observable was seen when the SYN1/SYN2 knockout mice was exhibiting its peak expression (Fassio et al, 2011). This information is indicative that in instances where both SYN1

and SYN2 were both simultaneously mutated, a strong epileptic phenotype was demonstrated.

Discussion and Conclusions

The aim of this review was to examine the relationship between epileptic activity and synapsin mutations and see if a strong correlation is present. Upon reviewing the studies throughout the course of this review in great detail, there is certainly a strong connection between mutations in Synapsins I and II and epilepsy. It was demonstrated that each male member who suffered from epilepsy in the four-generation family that Garcia et al examined through their work had an obvious mutation in their SYN1 polymorphism region. Likewise, the epileptic subjects in Lakhan et al's work had a significantly higher A>G mutation frequency than the control subjects, demonstrating that a mutation in SYN2 had a positive correlative relationship with the individuals who suffered from epilepsy. This topic is of vital importance because epilepsy is one of the most prevalent neurological disorders and there are currently only methods to suppress epileptic and seizure-like activity, but no way to completely cure any individual from having episodes. From a pharmacological perspective, a plethora of anti-epileptic drugs have been created, but it may be of interest and potential benefit in the future to examine creating a drug that prevents mutations in synapsins from occurring. However, a historical breakthrough such as this would require more work being done, specifically examining mutations in not just one or two of the known synapsins, but all three. Ultimately, additional research and further strides in this field have to continue being made in order to solve a key piece of concern regarding one of the most common and detrimental neurological disorders that we are currently aware of.

References

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