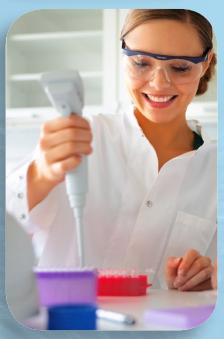
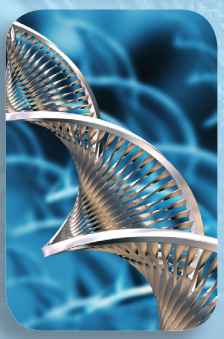
Modified anuroctonus scorpion toxin peptides as potent Kv1.3 potassium channel blockers

University of Debrecen

Researchers at the University of Debrecen have successfully improved the properties of anuroctoxin in inhibiting the Kv1.3 potassium channel by directed mutation. Research results suggest that the peptide toxins may have beneficial effects in the management of autoimmune diseases.





Challenge

Effector memory T cells, which are major contributors to the pathogenesis of several autoimmune diseases (rheumatoid arthritis, multiple sclerosis, type I diabetes), express Kv1.3 channels in much higher numbers than other T cell subtypes and consequently their proliferation relies acutely on the operation of these channels. The different channel expression pattern in other T cell subtypes allows for specific targeting of effector memory T cells. Thus, the progression of certain autoimmune diseases may be controlled with Kv1.3 blockers of high affinity and specificity, and these compounds could serve as the basis for the development of drugs for the treatment of autoimmune diseases in the future. This approach would offer great benefits over traditional immunosuppressive therapies, which make patients susceptible to infections due to their non-specific nature. Animal studies with other Kv1.3-blocking toxins have proven the feasibility of the method.

Technology

Peptide toxins from the venoms of various species, including scorpions, are known to be high affinity ion channel blockers. For a toxin to be available for potential therapeutic application, it is essential that it should only block the ion channel involved in the targeted function of the target cell without influencing other channels. Thus, for compounds developed for the treatment of T cell mediated autoimmune diseases, high selectivity for Kv1.3 is just as important a prerequisite as high affinity for the channel. Due to significant sequence and structural similarities among closely related voltage-gated potassium channels, highly selective toxins are quite difficult to generate.

The researchers undertook the improvement of the channel-toxin interaction by increasing the selectivity and affinity of anuroctoxin for Kv1.3, achieved by directed mutations in its sequence. Mutation positions and residues were determined based on thorough comparison of the sequence and blocking profile of numerous peptide toxins as well as consideration of interacting residues determined from docking simulations for other toxins. The inventors have successfully modified the scorpion toxin peptide in a way to improve its properties in inhibiting Kv1.3 potassium channel protein.

Faculty of Medicine

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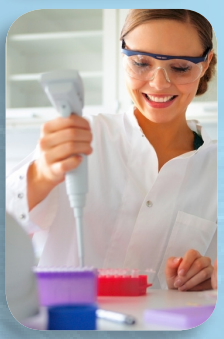

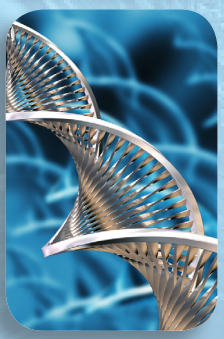

Development status

The affinity and selectivity of the natural molecule extracted from scorpion venom have been successfully improved through mutations. The researchers synthesized the mutated toxin peptide, and electrophysiological examinations were carried out with positive results. The first mutation introduced abolished the high affinity of the natural toxin for Kv1.2, a channel closely related to Kv1.3 and abundantly found in the nervous system, but caused a slight decrease in affinity for Kv1.3. Introducing the second mutation in the background of the first one restored the high affinity of the toxin for Kv1.3 while preserving the improved selectivity.
Recently, successful animal experiments have been performed with the synthesized wild-type anuroctoxin in order to test the inhibiting efficiency in a Delayed-Type Hypersensitivity test, which is a model for T cell-mediated autoimmune reactions. The synthetic wild-type toxin proved as effective in suppressing the DTH response as ShK-186, a toxin optimized for such applications and thoroughly tested in vivo in animal models. Due to the fact that the mutant toxin has the same affinity as the wild-type toxin, but is much more selective for Kv1.3, it is expected to be as effective as the wild-type without the potential side effects caused by cross reactions with other channels. This highlights the potential beneficial effects of the mutant toxin in the management of autoimmune diseases.

Benefits

- High affinity and selectivity of the modified anuroctoxin for blocking the Kv1.3 channel
- The Delayed-Type Hypersensitivity test has proven the concept of the invention

IP status

PCT I. phase has been started, the international application claims the priority of October 28, 2011. The IP rights are shared between the University of Debrecen (70%) and the University of Szeged (30%).

What we are looking for

A company interested in commercializing a peptide toxin with high affinity and selectivity for the Kv1.3 potassium channel.

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