Molecular Characterization of the Binding of Polyunsaturated Fatty Acids to a Voltage-Gated Potassium Channel

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In refractory epilepsy, a ketogenic diet (ample protein and low carbohydrate intake) has proven to be an effective treatment. Fatty acids, and in particular polyunsaturated fatty acids (PUFAs) have been identified as the key constituents in the anticonvulsant property of this diet. Here, we report on studies of this process using molecular simulations that show how PUFAs-enriched lipid bilayers interact with an integral voltage-gated ion channel, their enrichment on specific regions of the voltage sensor, and how this might help explain the selective stabilization of the open state of a voltage-gated K+ channel.

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explain the selective stabilization of the open state of a voltage-gated K+ enriched lipid bilayers interact with an integral voltage-gated ion channel, their activity was still recorded without PG for bilayers close to physiological membrane thickness (~27 Å), suggesting that mechanical stress may compensate for the absence of the negatively charged head group. Moreover, clustering could also have a regulating effect since appearance of coupled channel activity showing significantly higher conductance than what is expected for KcsA was observed in the presence of clusters.

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Kv1.3-Blocking Peptides from Parasitic Worms Exhibit Immunomodulatory Function

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Parasites have coexisted with their human hosts for thousands of years and are known mainly for their harmful disease-causing role in humans. However, probiotic worm therapy is beneficial in human autoimmune diseases, suggesting the existence of immunomodulators in parasitic worms. By screening a cDNA library and searching genome databases we identified a family of peptides in parasitic worms that share sequence similarity and evolutionary relatedness to potassium channel-blocking peptides secreted by venomous sea anemones. AcK1, a 51-residue secreted peptide of the hookworm Ancylostoma caninum, and BmK1, the C-terminal domain of a 413-residue zinc metalloprotease from the filarial worm Brugia malayi, share structural similarity to ShK and BgK peptides from sea anemones. These peptides block cloned and native human T-cell Kv1.3 channels at nanomolar to low micromolar concentrations. BmK2, an analog of BmK1, blocks Kv1.3 with an IC50 of 2 nM and exhibits >4000-fold selectivity for Kv1.3 over Kv1.1, Kv1.2, Kv1.6, Kv3.2, KCa3.1, K+3.1. These peptides suppress proliferation of effector memory T cells that use Kv1.3 channels to regulate membrane potential, without affecting other T cell subsets that are not dependent on Kv1.3. They inhibit cytokine production and suppress the in vivo delayed type hypersensitivity response. Our results provide a mechanistic basis for pro-biotic worm therapy in human autoimmune disease, and suggest that these related peptides or proteins could supplant the need for worm therapy.