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Molecular design as an efficient tool in generation of new potential therapeutic agents against calcium cytotoxicity

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Molecular design is a powerful tool that aims to take the most of the structural components of molecules to understand how can they interact and produce the effects that we observe. In our particular case, molecular design has been used to generate new therapeutic agents that help modulate the operation of a specific glutamate receptor and thus prevent negative effects generated by the overstimulation in degenerative processes of the nervous system. For that, we have worked with the ionotropic glutamate receptor type NMDA (NMDAR) which has been previously identified as a pharmaceutical target of importance in degenerative processes of the nervous system in which calcium is a cytotoxic agent for its high influx to the cell. For this work, our target was the GluN2B subunit of NMDA receptor in which interactions with proteins as D2R, DAPK1 and SRC have previously been identified could be involved in calcium excitotoxic processes. We designed and generated some peptides that could specifically inhibit these interactions. We also performed a comparative study of various peptide toxins from marine cones, called conotoxins, to design additional peptides that may interact with GluN2B subunit extracellular domain and get receptor inhibition by this route. By utilizing bioinformatics tools and molecular design, peptides interact with GluN2B subunit of the NMDA receptor and could generate a negative modulation of its operation, allowing the inhibition of the toxic imbalance of calcium in the cell.

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Dietary manipulation of gut microbial metabolites prevents autoimmune diabetes

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Diet and gut microbial ecology may underlie the increasing incidence of certain inflammatory diseases. Here, we found that key features of autoimmune diabetes in NOD mice, such as gender differences and protection *in MyD88-/-* NOD mice, correlated closely with blood and fecal concentrations of the short chain fatty acids (SCFAs) acetate and butyrate. We then used specialized diets to deliver high concentrations of acetate and butyrate to the colon and hepatic portal vein of NOD mice, when tolerance to islet antigens has already been broken. High acetate or butyrate yielding diets significantly reduced progression to diabetes, through effects on the colonic microbiota, improved gut epithelial integrity and reduced concentrations of IL-21 and TNFα. Both acetate and butyrate diets led to dramatically decreased numbers of autoreactive T-cells in lymphoid tissues. A high butyrate yielding diet promoted conversion of naive T-cells into *Foxp3*+ Treg cells *in vivo,* through histone modification at the *Foxp3* promoter that led to increased numbers of Treg cells in both the gut and the periphery. In contrast, an acetate yielding diet inhibited histone deacetylase-3 transcription in B-cells, which led to markedly reduced expression of CD86 and MHC-I and reduced capacity to expand autoreactive CD8+ T cells *in vivo*. Control of autoimmune T-cell frequencies and protection from diabetes relied in part on the metabolite-sensor GPR43, a receptor for both acetate and butyrate. Specialized diets that yield high acetate or butyrate may represent an effective non pharmacologic means to limit autoreactive T-cell numbers and prevent autoimmune disease progression.

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