A cure for drunkenness?

Enzymes are biocatalysts that mediate every biological process in living organisms. Most enzymes do not roam freely within the cell but are carefully positioned together within subcellular compartments along with complementary enzymes. This allows toxic intermediates generated by one enzyme to be promptly eliminated by another enzyme before it can diffuse into the cell.

Inspired by these clusters of complementary enzymes, a team of researchers led by Yunfeng Lu (University of California, Los Angeles) employed a new technique to assemble and encapsulate multiple enzymes with complementary functions within a thin polymer shell to form an enzyme nanocomplex (*Nat. Nanotechnol.* doi:10.1038/nnano.2012.264; published online 17 February 2013). To combine the enzymes, the researchers attached inhibitors of each enzyme to the ends of a single-stranded DNA scaffold. When the enzymes are mixed with the scaffold, they bind to their respective inhibitors and form the nanocomplex. Then a thin layer of polymer is grown around the nanocomplex to protect it. Finally, the DNA-inhibitor scaffold is removed so that the enzymes are free to catalyze reactions.

Excessive consumption and abuse of alcohol is associated with a range of organ injuries and social problems. The scientists constructed a nanocomplex that could be used to reduce blood alcohol levels as an antidote and prophylactic for alcohol intoxication in mice. The nanocomplex was constructed to combine alcohol oxidase (AOx), which breaks down alcohol but produces toxic hydrogen peroxide (H_2O_2) as a byproduct, and catalase (Cat), which is highly active and specific in decomposing H_2O_2. By packaging them together in the complex, Cat effectively removes the generated H_2O_2 and prevents it from inactivating the AOx.

In prophylactic studies, mice that were fed a combination of alcohol and the nanocomplex had significantly reduced blood alcohol content (BAC). The reduction increased over time and was greater than in mice that were fed alcohol with just one of the enzymes or in mice that were fed alcohol and both enzymes in separate complexes. A dose-dependence study suggested that BAC decreased with increasing doses of the nanocomplex. To test whether the nanocomplex could act as an antidote to alcohol intoxication, the nanocomplex was injected into the tail vein of intoxicated mice. The treated mice had the largest BAC reduction and showed the lowest levels of an enzyme biomarker for liver damage.

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The authors propose that such enzyme complexes could be built for a variety of applications, given the vast range of enzymes that are currently or potentially available.

Kara Rosania

INSIGHT INTO THE NEUROLOGY OF ANGELMAN SYNDROME

Results recently published in *PLoS Biology* (**11**, e1001478; 2013) elucidate the neurological disruptions that occur in Angelman syndrome and introduce a compound that can rescue the disruptions, restoring neural function in mice. John Marshall (Brown University, Providence, RI), senior author of the article, warned that it is too soon to tell when a clinical therapy might be available. But the results hold promise for those who have the disease.

Angelman syndrome is characterized by development delays, seizures, movement disorders, speech impediments and, often, features of autism. It is a genetic disorder caused by a lack of function of the enzyme Ube3A. The normal role of Ube3A is to regulate degradation of the synaptic protein Arc in the brain, limiting its availability. In the absence of functional Ube3A, however, levels of Arc are elevated. Arc hinders synaptic development in the hippocampus by interfering with PSD-95, which is required for the signaling activity of brain-derived neurotrophic factor (BDNF), a growth factor involved in long-term potentiation (LTP). BDNF activity strengthens neural connections or synapses that are essential to learning and memory formation. Hence, by inhibiting BDNF activity, Arc weakens these processes. "I think we are really beginning to understand what's going wrong. That's what's very exciting," said Marshall in a press release.

With this understanding of the interaction between Arc, PSD-95, BDNF activity and LTP, Marshall and his team turned their attention to the compound CN2097, a synthetic, bridged cyclic peptide that enhances BDNF activity and protects neurons from damage from stroke and multiple sclerosis. CN2097 binds to PSD-95, protecting it from interference by Arc and, in turn, restoring BDNF activity and strengthening synapses. When tested in a mouse model of Angelman syndrome, CN2097 improved the induction of LTP, leading the study authors to suggest that the compound might offer an approach to reversing cognitive dysfunction.

The team has not yet tested whether CN2097 administration improves cognitive or behavioral function in mice carrying the genetic defect that causes Angelman syndrome. "Can we actually rescue learning deficits?" Marshall asked. "That would be the next stage to test. We haven't gotten that far yet." Another limitation to further development of CN2097 as a treatment for Angelman syndrome is its rapid breakdown in the body; the drug might require frequent administration to maintain its efficacy. But the research is encouraging, said Marshall. "We think we are on the right track."

Monica Harrington