The work in our laboratory is focused on the molecular mechanism by which nerve cells communicate with each other at specialized connections, or synapses. Recent work in the laboratory has supported the idea that many diseases of the brain result from deficits in communication between nerve cells or synapses.

For close to a decade, pharmaceutical researchers have been pursuing compounds to activate a key nicotine receptor that plays a role in cognitive processes. Triggering it, they hope, might prevent or even reverse the devastation wrought by Alzheimer’s disease. Researchers in Heinemann’s lab, however, whose group first identified the brain receptors that respond to nicotine, have discovered that when the receptor, alpha-7, encounters beta amyloid, the toxic protein found in the disease’s hallmark plaques, the two may actually go rogue. In combination, alpha-7 and beta amyloid appear to exacerbate Alzheimer’s symptoms, while eliminating alpha-7 seems to nullify beta amyloid’s harmful effects.

Alpha-7 is expressed all over the brain, in all mammals, which means that it is probably essential, but investigators have not yet discovered for what. Intrigued by earlier studies showing that beta amyloid seemed particularly drawn to the alpha-7 nicotinic receptors, Heinemann and his team hypothesized that the receptors mediate beta amyloid effects in Alzheimer’s disease. To test their theory, they crossed mice engineered to lack the gene for alpha-7 with a mouse model for Alzheimer’s disease, which had been genetically engineered to overexpress amyloid precursor protein (APP), an antecedent to beta amyloid. They then put the offspring through a series of memory tests. Surprisingly, those with both mutations—too much APP and no gene for alpha-7—performed as well as normal mice. The Alzheimer’s mice, however, which had the alpha-7 gene and also overexpressed APP, did poorly on the tests. Pathology studies revealed the presence of comparable amounts of plaque in the brains of both types of mice, but in those lacking the alpha-7 gene, they appeared to have no effect. Similar disparities were evident in measurements of the synaptic function underlying learning and memory.

These findings, which suggest a completely different target for potential Alzheimer’s drugs than those that have been tried, could have important implications for researchers seeking to combat the disease.

For more information, please visit www.salk.edu/faculty/heinemann.