Barrow Neurological Institute researchers have identified a novel receptor in the brain that is extremely sensitive to beta-amyloid peptide (AB) and may play a key role in early stages of Alzheimer's disease.

Published in the *Journal of Neuroscience*, the research lead by Jie Wu, MD, PhD, has identified a new candidate for therapeutic intervention in Alzheimer's.

The novel receptor was found in the basal forebrain, an area of the brain that plays a critical role in memory and learning and is one of the first areas of the brain to degenerate with Alzheimer's. That degeneration is associated with losses of the chemical messenger, acetylcholine, and some of the molecules that translate acetylcholine's messages, called nicotinic receptors. The forming of large aggregates or plaques of AB also is a hallmark of Alzheimer's disease. While these two features have been under examination in Alzheimer's research, it is not clear how they interrelate.

At Barrow, Dr. Wu and his colleagues made the unexpected finding during a study examining effects of AB on basal forebrain nicotinic receptors. They first found that acetylcholine signaling at those receptors was highly sensitive to blockage even by low levels of AB. They also found that AB as small aggregates -- and not large plaques of AB -- had this same blocking effect. They next found that the type of nicotinic
receptors showing this high sensitivity to AB has a different composition than other nicotinic receptor types previously identified and shown to be less sensitive to AB.

"We now believe that most of the nicotinic receptors in the basal forebrain have this unique composition and high sensitivity to AB," says Dr. Wu. "Our hypothesis is that as AB begins to increase, it first blocks acetylcholine signaling at these receptors, perhaps triggering events that eventually lead to neurodegeneration."

"This is the first time that AB has been proven to block acetylcholine at a concentration that occurs in Alzheimer's brain and thus could be pathologically relevant," says Ron Lukas, PhD at Barrow, who was part of the research team. "We also helped to implicate small aggregates of AB as being pathologically relevant."

"If we can identify a drug that would selectively keep the unique forebrain nicotinic receptors active even in the presence of AB, or block the effects of AB on those receptors, then we might be able to stave off the early steps in the Alzheimer's disease process," says Dr. Lukas.

Source: St. Joseph's Hospital and Medical Center


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