Researchers find new way to use antibodies to carry drugs across the blood-brain barrier

26 May 2011, by Bob Yirka

(Medical Xpress) -- In what appears to be a major breakthrough in the treatment of Alzheimer's and other diseases that affect the brain, researchers from Roche Genentech have succeeded in engineering an antibody that can be used to carry therapeutic drugs across the so called blood-barrier in the brain, which can then block substances such as beta-secretase 1, thereby preventing the buildup of the amyloid beta proteins that cause the creation of sticky plague seen in the brains of Alzheimer's sufferers. Publishing their results in two papers in *Science Translational Medicine*, the group describes how they engineered an antibody normally used to carry iron in the blood to the brain, to allow therapeutic drugs to tag along for the ride, leading to a big increase in the amount of the drug that is able to make it across the membrane and fluids barriers that serve to protect the brain from infection.

Led by researcher Ryan Watts, the team set out to find a way to deliver drugs already known to be effective in treating brain ailments, in a more effective way, as currently, only about 0.1% of such drugs make it past the brain-blood barrier, requiring patients to take very large amounts of drugs over a periodic basis, which of course leads to a lot of negative side effects. To overcome this hurdle, the team focused on transferrin receptors, which are the parts of antibodies that are able to carry iron across the barrier; figuring if they could come up with a way to have those very same receptors also carry across drugs, they'd have the key to overcoming a major barrier to treating brain ailments.

After much research and effort, it appears the team has accomplished its goal; at least in animals that have been tested using the new method, and they've done it by figuring out a way to make the transferrin receptors less "sticky." Up till now, getting the receptors to carry substances such as drugs, wasn't an issue, it was getting them to let go of them once they reached the brain that was tricky. And now, based on the results shown in their paper, (the amount of amyloid in the brains of test mice after delivery of a drug was cut in half) it appears this is exactly what the team has accomplished.

The next step of course, will be to find out if what they've developed will work in human beings. If so, it's likely a major milestone will have been reached in the treatment of brain ailments, though the team is quick to point out, it's not yet known for certain if the plague that builds up in the brains of people afflicted with Alzheimer's is actually the cause of the disease, or only a side-effect. In any case, if the process works as hoped, it could then possibly be used in the treatment of a whole host of other brain ailments such as Parkinson's disease, autism or even perhaps schizophrenia.

More information: Paper 1: A Therapeutic Antibody Targeting BACE1 Inhibits Amyloid-? Production in Vivo, Sci Transl Med 25 May 2011: Vol. 3, Issue 84, p. 84ra43 DOI: 10.1126/scitranslmed.3002254

ABSTRACT

Reducing production of amyloid-? (A?) peptide by direct inhibition of the enzymes that process amyloid precursor protein (APP) is a central therapeutic strategy for treating Alzheimer's disease. However, small-molecule inhibitors of the ?-secretase (BACE1) and ?-secretase APP processing enzymes have shown a lack of target selectivity and poor penetrance of the blood-brain barrier (BBB). Here, we have developed a high-affinity, phage-derived human antibody that targets BACE1 (anti-BACE1) and is anti-amyloidogenic. Anti-BACE1 reduces endogenous BACE1 activity and A? production in human cell lines expressing APP and in cultured primary neurons. Anti-BACE1 is highly selective and does not inhibit the related enzymes BACE2 or cathepsin D. Competitive binding assays and x-ray crystallography indicate that anti-BACE1 binds noncompetitively to an

exosite on BACE1 and not to the catalytic site. Systemic dosing of mice and nonhuman primates with anti-BACE1 resulted in sustained reductions in peripheral A? peptide concentrations. Anti-BACE1 also reduces central nervous system A? concentrations in mouse and monkey, consistent with a measurable uptake of antibody across the BBB. Thus, BACE1 can be targeted in a highly selective manner through passive immunization with anti-BACE1, providing a potential approach for treating Alzheimer's disease. Nevertheless, therapeutic success with anti-BACE1 will depend on improving antibody uptake into the brain.

Paper 2: Boosting Brain Uptake of a Therapeutic Antibody by Reducing Its Affinity for a Transcytosis Target, Sci Transl Med 25 May 2011: Vol. 3, Issue 84, p. 84ra44 DOI: 10.1126/scitranslmed.3002230

ABSTRACT

Monoclonal antibodies have therapeutic potential for treating diseases of the central nervous system, but their accumulation in the brain is limited by the blood-brain barrier (BBB). Here, we show that reducing the affinity of an antibody for the transferrin receptor (TfR) enhances receptor-mediated transcytosis of the anti-TfR antibody across the BBB into the mouse brain where it reaches therapeutically relevant concentrations. Anti-TfR antibodies that bind with high affinity to TfR remain associated with the BBB, whereas lower-affinity anti-TfR antibody variants are released from the BBB into the brain and show a broad distribution 24 hours after dosing. We designed a bispecific antibody that binds with low affinity to TfR and with high affinity to the enzyme ?-secretase (BACE1), which processes amyloid precursor protein into amyloid-? (A?) peptides including those associated with Alzheimer's disease. Compared to monospecific anti-BACE1 antibody, the bispecific antibody accumulated in the mouse brain and led to a greater reduction in brain A? after a single systemic dose. TfR-facilitated transcytosis of this bispecific antibody across the BBB may enhance its potency as an anti-BACE1 therapy for treating Alzheimer's disease.

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