Update on Elan vaccine for Alzheimer’s disease

Ever since a phase II trial of Elan and Wyeth’s experimental vaccine for Alzheimer’s disease (AD) was halted in Jan, 2002, after some patients developed meningoencephalitis (Lancet Neurol 2003; 1: 3), researchers at the two companies have been racing to find out which part of the synthetic protein AN-1792 was responsible for triggering the inflammatory response. On Nov 9 they reported at the Society for Neuroscience meeting (New Orleans, LA, USA) that a fragment of AN-1792 can induce the production of antibodies to amyloid-β peptide (Aβ) deposits in brain tissue of patients with AD without triggering inflammation, raising hopes that a modified form of AN-1792 still holds promise as a vaccine.

AN-1792 contains a form of Aβ that is 42 amino acids in length, which proved effective in early trials at clearing Aβ plaques from the brains of patients with AD. So, Mike Lee (Elan, San Francisco, CA, USA) and colleagues made a series of 10-amino acid fragments of AN-1792, to find out which portion is recognised by the patient’s antibodies, producing the therapeutic effect. They found that all patients who raised antibodies to AN-1792 actually raised antibodies to one very specific part of it—the tail end of Aβ. That finding contradicted earlier studies that had suggested that patients’ antibodies only recognised aggregates of AN-1792, thought to resemble the clumps of Aβ that occur in AD brains.

They then looked to see if the antibody response in those patients who had the inflammatory response differed from those who did not, and found that it was identical. That suggested that some other immune mechanism had triggered the meningoencephalitis. “The meningoencephalitis was suppressed to be caused by the auto-reactive Th1-type T cells”, says Hideo Hara of the National Institute for Longevity Sciences in Aichi, Japan, adding that Th2-type T cells are needed to raise the antibody response. “If the team… has developed a vaccine with the new fragment of the protein plus adjuvant that induces only the Th2-type T cells and does not induce Th1-type T cell immune responses, it will work without the side-effects of meningoencephalitis”, he says.

Hara is leading a team working on an oral vaccine that he believes will bypass the Th1 T cell-mediated response entirely. They have shown that their approach, which uses an adeno-associated virus as a vector, is effective in mice, and are now testing it in ageing monkeys. “The production of antibodies lasts at least 6 months after only one oral administration, which may be of benefit for the patients because they do not need to receive frequent intramuscular injections”, says Hara. He adds that it may be safer than injecting viral vectors into muscles, because the turnover of epithelial cells lining the gut is so rapid that the vector cannot remain in the body for long.

Laura Spinney

Cocaine use may damage dopaminergic system

Chronic cocaine use suppresses myelin-related genes and increases the production of the neuronal protein α-synuclein, according to two new studies that were presented at the Society for Neuroscience annual meeting (New Orleans, LA, USA, Nov 8–12). One study could explain the subtle deficits in thought and movement experienced by ageing addicts, while the other group of researchers predict that this population will see a wave of Parkinson’s disease in the future.

In the first study, Dawn Albertson (Wayne State University, Detroit, MI, USA) and colleagues analysed post-mortem tissue from the nucleus accumbens of 10 cocaine users and 10 drug-free controls for differences in patterns of gene expression by use of microarray technology.

During their search, says Albertson, they made the “totally unanticipated” discovery that the expression of at least seven myelin-related genes was decreased in the addict group, and in some cases dramatically decreased. These included genes encoding myelin basic protein, proteolipid protein, and myelin associated oligodendrocyte protein. Anatomical studies with antibodies to bind to myelin basic protein later confirmed that there was a substantial decrease in the number of myelin-producing cells, or oligodendrocytes, in the nucleus accumbens of the cocaine users.

Albertson says these changes could affect the rapid transmission of information in the nucleus accumbens of addicts, also known as the brain’s “pleasure centre”, and could be associated with the subtle cognitive and motor deficits experienced by chronic users. However, she now wants to determine the sequence of events in the brain: “Is it a phenotype of individuals that predisposes them to self-medicate with cocaine, or is it the cocaine that actually causes this to occur?”, she asked.

Deborah Mash (University of Miami School of Medicine, FL, USA) and colleagues, meanwhile, have found a threefold increase in α-synuclein concentrations in dopamine cell groups in the brains of cocaine users at post mortem, compared with drug-free controls. This increase was significantly correlated with raised concentrations of dopamine transporter proteins in the striatum, which receives projections from the dopamine cell bodies.

Since cocaine blocks the re-uptake of dopamine, the researchers conclude that this represents a compensatory response of the addicted brain. Although the normal functions of α-synuclein are not well understood, Mash thinks that this altered response could predispose addicts to neurodegenerative changes in dopamine neurons. “We have started to see cases of parkinsonism in cocaine addicts in their fifties”, she said. “I suspect that more cases will start to emerge.”

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