

NEWS

Old drugs to treat new variant Creutzfeldt-Jakob disease

The antimalarial drug quinacrine and the antipsychotic chlorpromazine prevent the conversion of normal (PrP^c) to abnormal (PrP^{sc}) prion protein, according to in-vitro research published by Stanley Prusiner's group this week. In light of these preliminary results, two patients with Creutzfeldt-Jakob disease (CJD) have been treated with quinacrine at the University of California, San Francisco, using compassionate use as a justification. "We are planning a treatment trial in the fall with three different arms. Quinacrine alone and quinacrine in combination with chlorpromazine will be tried", says Bruce Miller, one of the clinical investigators.

The preliminary in-vitro work was done by Carsten Korth and co-workers who used a common model for prion disorders—a cultured mouse neuroblastoma cell line (ScN2a) infected with PrP^{sc}—to show that 6 days of treatment with quinacrine or chlorpromazine reduced the conversion of PrP^c to PrP^{sc} (*Proc Natl Acad Sci* 2001; **98**: 9836–41). The investigators screened a wide variety of drugs known to cross the blood-brain barrier, but found quinacrine and chlorpromazine to be the most effective at halting, and even reversing, PrP^{sc} infection in vitro.

They also determined the structure-activity relations for a number of acridine and phenothiazine

derivatives, and identified the molecular characteristics that convey potency for inhibition of PrP^{sc} formation.

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Stanley Prusiner

This is not the first time that quinacrine has been tested for its antiprion effects. Last year, researchers from Kyushu University (Japan) and the National Institute of Allergy and Infectious Diseases (Hamilton, MT, USA) reported similar effects of quinacrine in the ScNB neuroblastoma cell line (*J Virol* 2000; **74**: 4894–97).

Quinacrine has been used in humans for over 60 years as a treatment for malaria and can be administered orally at high doses on a daily

basis. However, chlorpromazine, although less potent than quinacrine in vitro, may prove to be a better alternative as it crosses the blood-brain barrier more readily.

"These tricyclic compounds, with their particular side-chain, constitute a new class of antiprion agents", says Barnaby May (University of California, San Francisco, CA, USA), one of the investigators. Importantly, these drugs have already been widely administered for other indications so their pharmacokinetics, toxicity and safety have been established. According to Korth, "these compounds are in clinical use and are known to cross the blood-brain barrier. Therefore, they are immediate candidates for the treatment of CJD. Their clinical value remains to be established, but even if clinical trials are not positive, new antiprion lead compounds have been introduced".

However, Miller points out that this work is still in its most preliminary stages. "I want to emphasise how far we are from knowing whether or not this trial will be beneficial. It would be very sad if we gave patients false hopes about a treatment that is so far from proven efficacy."

John Collinge, head of the MRC Prion Unit in London, adds that his department's research programme is well underway, pursuing several distinct strategies for the treatment of CJD. The unit hopes to begin its own clinical trials next year. "There is a strong case for proceeding to clinical trials for CJD at a much earlier stage than for other disorders, since they are rapidly progressive and invariably fatal disorders. Understandably, families are keen to access urgently any new treatments available. However, properly controlled trials are needed to establish the usefulness of any of these treatments. If we use them outside such a trial without systematic specialised monitoring of progress we may learn little about their efficacy, benefits and hazards in what remain, thankfully, rare diseases", says Collinge.

Rebecca Love

The antibody approach

In a separate study published in *Nature* this week, the Prusiner group investigated seven different recombinant antibodies raised to various parts of the normal PrP^c protein. They exposed a mouse neuroblastoma cell line (ScN2a) infected with PrP^{sc} to varying concentrations of each antibody for 7 days (*Nature* 2001; **412**: 739–43), and measured the amount of PrP^{sc} protein present. D18, the most potent antibody, prevented corruption of PrP^c to PrP^{sc} and also cleared pre-existing PrP^{sc} in a dose-dependent manner. Removal of D18 after 2 weeks of treatment left cultures PrP^{sc}-free for an additional 4 weeks. The antibody is thought to bind to PrP^c molecules on the cell surface hindering the docking of the PrP^{sc} template or co-factor involved in the conversion of PrP^c to PrP^{sc}. "This finding offers hope of therapeutic success in the treatment of established disease. We must now seek to establish if these promising effects can be replicated in animal models in both prion disease prevention and therapy", says Anthony Williamson (Scripps Research Institute, La Jolla, CA, USA), one of the investigators. However, drawbacks of this treatment approach include the short antibody half-life (28 hours for D18) and problems with transport across the blood-brain barrier.