Antibiotic progress for disease that causes half a million deaths a year

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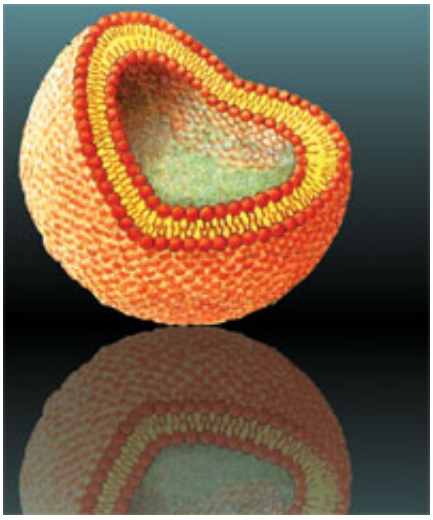

Cartoon of a liposome. Credit: UT-Houston Medicine, 2007

(PhysOrg.com) -- Scientists are making progress in their quest to find an improved antibiotic for a strain of meningitis that results in over half a million deaths a year worldwide. The fungal disease Cryptococcal Meningitis is especially rife in AIDS patients and there are fears that if new drugs cannot be found, it could become untreatable. The results are published in one of the most respected journals in the field of membrane biology - Biochimica et Biophysica Acta – Biomembranes. Further experiments will be carried out at STFC's ISIS neutron source this week.

Cryptococcal Meningitis is diagnosed in nearly a million people a year

worldwide, mainly in AIDS patients but also in others with defects in their cell mediated-immunity. More than 600,000 of these cases lead to fatalities. Currently, there is no vaccine for Cryptococcal Meningitis. Unlike most other strains of the disease, it is not passed from person to person, but is actually acquired from the environment, possibly by exposure to birds. The disease is most prominent in Sub-Saharan Africa but is also known to be on the increase in areas such as Thailand and India.

With funding from the Engineering and Physical Sciences Research Council, scientists from King's College London have been using neutrons to look at the effects of the antibiotic Amphotericin which is currently used to treat Cryptococcal Meningitis. They hope this will help them devise new and more effective treatments, in particular for the disease-causing fungi that have developed a resistance to the drug.

"Such an approach, of course, requires that we fully understand how Amphotericin works, and unfortunately this is not the case", said David Barlow – the lead researcher from King's College London.

"We do know that the drug has little effect on the cells in a human because these cells are surrounded by membranes containing cholesterol. We also know that the drug exerts its effects on fungi because their cells do not contain cholesterol, but instead have a related steroid, ergosterol. However it is quite unclear how this difference between human and fungal cell membranes matters to the workings of Amphotericin."

Research published in the journal *Biochimica et Biophysica Acta – Biomembranes* shows that Amphotericin can insert itself into cell membranes regardless of whether they contain cholesterol, ergosterol, or no sterol at all, and the resulting changes in the structure of the membrane seem to be the same for all three systems. This means the reason for the drug having less impact on human cells than fungal cells

cannot purely be down to the fact that human cells contain cholesterol – other factors must be at play.

What seems more likely is that the drug interacts more rapidly with fungal cells than human cells, or that the structures it forms after inserting in to their membranes are different for the two types of cell.

“We're now going on to investigate the first of these possibilities, and during our next experiments at ISIS, we plan to look for differences in the speed with which the drug enters human and fungal cell membranes”, said David Barlow. “The more information we can gather about how this complex system works, the more likely we are to be able to develop a new antibiotic that will be as effective as Amphotericin has been until recently”.

In addition to Cryptococcal Meningitis, Amphotericin is also used to treat infections such as the tropical disease Visceral Leishmaniasis.

More information: Download the full scientific paper.

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