Sleeping sickness treatment mystery unlocked

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(Medical Xpress)—Scientists at the Universities of Dundee and Glasgow have discovered how drugs that have been used for 60 years to kill the parasite that causes sleeping sickness actually work.

Research has revealed that the drugs used to attack *Trypanosoma brucei* enter through pores in the parasite's cells known as aquaporins which function as water channels.

It is the first time that drugs have been shown to enter cells through aquaporins and this may have major implications for drug delivery in other diseases.

Dr Harry de Koning, a Reader of Biochemical Parasitology at the University of Glasgow who has been studying drug resistance mechanisms in pathogenic protozoan parasites, said: 'This research is a breakthrough in understanding how the drugs used to attack the sleeping sickness parasite get inside their target: like spies into an enemy castle they enter through a water channel.

'The discovery heralds a new paradigm for drug uptake by cells, as this is the first time that drugs have been shown to enter cells through aquaporins.

'Although there have been some reports of these channels being permeable to inorganic ions or small molecules, this is the first detailed report of an aquaporin acting as a genuine transport protein rather than a

passive channel for mainly water.'

The Glasgow researchers, in collaboration with Professor David Horn of the University of Dundee, identified a genetic link between a single parasite gene and its susceptibility to the drugs pentamidine and melarsoprol, which were first introduced in the 1930s and 1940, respectively.

The gene in question coded for one of the trypanosome's channels for water and glycerol, aquaporin 2 (TbAQP2).

Aquaporins are found in virtually all organisms, from bacteria to humans, selectively mediating the uptake or release of water and/or glycerol, thus maintaining osmotic equilibrium.

At least thirteen different aquaporins are expressed in various human tissues, and hundreds of others have been identified in other species, comprising a large and highly conserved gene family. Their vital importance to life was recognised with a Nobel Prize, in 2003, to the discoverer of the first aquaporin gene.

The genome of Trypanosoma brucei, the protozoan parasite that causes African sleeping sickness, contains three such aquaporin genes, all of which appeared to be conventional water/glycerol channels.

The team at the University of Glasgow have now established that one of these channels, TbAQP2, uniquely, acts as a conduit for two drugs that are still essential for the treatment of sleeping sickness today.

They found mutations, rearrangements or loss of the TbAQP2 gene in every drug resistant strain that was examined, and were able to reverse this by introducing the original TbAQP2 gene back into these parasites.

Painstaking investigations into drug transport in parasites expressing original or mutant TbAQP2 channels showed that this protein actually also functions as a highly efficient transporter for pentamidine, used for the early stage of the disease, and melarsoprol, which is used for the late, cerebral stage.

Finally they showed that the introduction of TbAQP2 into a different parasite species, Leishmania mexicana, made those parasites more than 1000-fold more sensitive to melarsoprol.

Dr De Koning said, 'Although the phenomenon of melarsoprol/pentamidine cross-resistance was first described in 1951 it had never been satisfactorily explained. The current study, published in the *Journal of Antimicrobial Chemotherapy*, by identifying and characterising the melarsoprol/pentamidine transporter, finally resolves this vital issue.

'As virtually all living cells express aquaporins, this discovery has potentially far-reaching implications for cellular transport and permeation mechanisms, potentially impacting on our understanding of drug distribution in many different diseases.'

More information: Read the complete paper: jac.oxfordjournals.org/content … dkt442.full.pdf+html

Provided by University of Dundee