

Crossing the blood-brain barrier: drug delivery to the brain is still elusive

In this third article in our series looking at developments in drug technologies, **Jenny Bryan** describes the development of techniques to get drugs across the blood-brain barrier

Drugs can only cross the blood-brain barrier by passive diffusion or with the help of transporters

High-tech wizardry is boosting drug delivery to many parts of the body. But the brain is proving a formidable adversary for those intent on designing new medicines to treat central nervous system diseases such as epilepsy, Alzheimer's disease, schizophrenia and brain tumours. Specifically, the endothelial cells that form the capillaries of the brain are in no hurry to stop acting as the so-called blood-brain barrier (BBB), despite the ever more ingenious efforts of pharmaceutical scientists to overwhelm them.

David Begley, who jointly runs the Blood Brain Barrier Research Group at King's College London, explains that, in contrast to the open endothelium of the peripheral circulation, the tight junctions between the endothelial cells of the brain's capillaries make it impossible for anything to get into the brain around the cells. Everything must go across the endothelial cell, either by passive diffusion or with the help of transporters, some of which work on the luminal membrane of the endothelial cell and others on the abluminal membrane which is in contact with brain cells.¹

Traditionally, pharmaceutical companies have chosen uncharged, lipophilic com-

pounds as CNS drugs because they have the greatest chance of getting across the BBB. But Dr Begley predicts that a growing understanding of its function and molecular biology will open the way for new delivery strategies over the next few years.

Early methods

Early efforts to manipulate the BBB in favour of drug delivery focused on prising apart the tight junctions between the endothelial cells. Hypertonic solutions introduced into the circulation via the carotid artery essentially shock the cells and make them shrink so that the junctions open up. This provides a window of about 30 minutes during which a CNS drug can be administered, also through the carotid artery. But the mechanism is non-specific and, during treatment, the brain is open to other, potentially toxic, substances in the blood.

Novel transport systems

Using the BBB's own transporters has proved a popular option. Valproic acid, L-dopa, baclofen and gabapentin all use endogenous transporters. But considerable effort over the past few years has gone into developing novel transport systems, such as nanoparticles and liposomes, with or without monoclonal antibodies as targeting mechanisms.

The greatest success with nanoparticle delivery — some would say the only success — has been with the anticancer agent, doxorubicin. Preclinical studies reported earlier this year showed that rats with glioblastomas had longer survival times when their tumours were treated with doxorubicin bound to polysorbate-coated nanoparticles, 200–400nm in diameter, than when they were treated with other formulations of doxorubicin.²

Advectus Life Sciences, based in Vancouver, is collaborating with researchers at two US universities to perform preclinical and drug stability tests on Nanocure, its nanoparticle formulation of doxorubicin, and hopes that it will get "fast track" attention from the Food and Drug Administration.

Advectus is also investigating the possibility of using its nanotechnology for drug delivery of the anti-infective agent, dapsone, into the CNS as a potential treatment for Alzheimer's disease.

NanoPharm AG, based in Magdeburg, Germany, has close links with the Frankfurt/Moscow team that carried out the promising rat studies with doxorubicin nanoparticles, and is looking for partners with which to develop its own Nanodel particles.

But the pharmaceutical industry is sceptical about the potential of nanotechnology to

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deliver in CNS diseases. Adam Dudley, associate director of drug metabolism and pharmacokinetics at AstraZeneca in Wilmington, US, points out that many companies, including AstraZeneca, spent several years investigating the potential of nanoparticles and other novel delivery technologies for CNS drugs.

"Nanoparticles have to be given intravenously and, unless coated with a surfactant, are cleared quickly by the liver. This makes them a fairly inefficient and therefore expensive technology," he says.

Passive diffusion and efflux

Instead of working on novel transport systems to get their drugs into brain cells, companies with strong CNS research programmes, such as AstraZeneca and UCB, are using tried and tested methods, like ensuring adequate passive diffusion rates using synthetic medicinal chemistry, for getting drugs across the BBB.

"By using drugs that rely on passive diffusion, we can establish a rapid equilibrium between plasma and brain levels. This ensures a lower risk of poor or variable CNS exposure than if we use active transport systems," he says.

But the mechanism by which drugs get into the brain is only part of the story. Dr Dudley explains that, even if a small fraction of a compound gets across the BBB, a high level of potency and receptor occupancy is what counts. This is difficult to measure in humans, but biomarkers, for example in the cerebrospinal fluid, can be checked to ensure that the right concentration of a drug is getting into the brain to drive its clinical efficacy.

Having saved their money on high-tech delivery systems, the pharmaceutical industry

is investing in research on the efflux mechanisms in the BBB that actively eject drugs before they can reach their target. Perhaps the most important of these is P-glycoprotein — a transporter on the luminal membrane of endothelial cells in the brain — which first came to researchers' attention when they realised that even some highly lipophilic molecules were not getting across the BBB as easily as expected.

Intensive research into P-glycoprotein over the past five years has confirmed its affinity for lipophilic compounds, particularly flat molecules with amines in their structure, says Dr Dudley. Animal models and cell systems are now used to screen new compounds to see if they are a substrate for P-glycoprotein.

"Some companies stop research on a new compound as soon as they see it is affected by P-glycoprotein but we prefer to try to modify the structure to see if we can get it past the efflux mechanisms," Dr Dudley explains.

Henrik Klitgaard, director of preclinical CNS research at UCB Pharma in Brussels, Belgium, agrees that efflux mechanisms are a big issue for CNS drug research, especially in epilepsy.

"Drug refractory epilepsy is due largely to the fact that most anti-epilepsy drugs get across the blood-brain barrier but then are actively transported out by mechanisms like P-glycoprotein," he says.

In fact, researchers at the Institute of Neurology in London last year published results of a pharmacogenomic study showing that epilepsy patients with a specific polymorphism in the P-glycoprotein gene were more likely to be resistant to anti-epilepsy

drugs than patients who did not have the marker.³

UCB's own epilepsy drug, levetiracetam, and its follow-up compounds now in early phase clinical trials, are not targeted by P-glycoprotein, and this is thought to account for the relatively low levels of resistance to levetiracetam seen so far in clinical practice.

Poor efficacy is not the only reason to try to avoid drugs that are targeted by efflux mechanisms, says Dr Klitgaard: "If you have a compound that is actively transported out, then you need higher plasma concentrations to achieve a steady state in the brain, and that is likely to give you more side effects."

A number of P-glycoprotein inhibitors have been used in phase I and II trials of anti-cancer drugs in an effort to improve their efficacy against brain tumours. But, as with drugs that open up the tight junctions between endothelial cells, the adverse effects of disturbing the BBB proved greater than the benefits.

The time for novel drug delivery strategies to the brain will come, say those actively involved in research, but it is not here yet.

References

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