CROSSING THE BLOOD BRAIN BARRIER (BBB)

WHICH ROUTE TO TAKE?

An expert panel/roundtable hosted by Aptar Pharma Prescription Division

Delivering solutions, shaping the future.
Aptar Pharma recently hosted an expert panel/roundtable on the various approaches to treating central nervous system (CNS) diseases. This international scientific forum was held in Paris, France on December 5th, 2014. The roundtable was organized to explore and exchange views on the challenges, approaches and opportunities that exist with regard to effectively crossing the blood brain barrier (BBB) and successfully treating a host of CNS diseases.

A large number of therapeutic areas fall within the CNS drug delivery arena, including Alzheimer’s disease, motor neuron disease, CNS trauma, Huntington’s disease, Parkinson’s disease and multiple sclerosis, Depression Schizophrenia, Sleep disorders etc. Currently it is estimated that drug delivery technologies used in applications for the CNS market total about 10Bn$ (2014) and this is predicted to grow to 22.5Bn$ by 2018 (1).

During this one-day meeting the experts shared their knowledge and debated several key themes, structured around the following subject areas:

- Understand the background and unmet medical needs.
- Investigate the various routes by which drugs can cross the BBB.
- Explore the pros & cons of various approaches currently being undertaken to deliver drugs to the CNS.

Invited guests came from a variety of backgrounds ranging from front-line neurosurgeon and clinicians to academic researchers as well as members of start-up companies in the CNS drug delivery field.

The summary of some of the discussions held, detailed below, reflects the views of our invited experts. Every attempt has been made to express the overall consensus of views as accurately as possible.

A large number of therapeutic areas fall within the CNS drug delivery arena, including Alzheimer’s disease, motor neuron disease, CNS trauma, Huntington’s disease, Parkinson’s disease and multiple sclerosis.

In order to improve existing CNS therapies and explore new ways of treating these disabling diseases, it is important to understand the role of the BBB and why it presents a particular problem for CNS drug delivery (2). The specific blood vessels that provide oxygen and nutrients to the human brain can reach up to a total length of 644 km, the distance between Paris and Munich (see Figure 1). It is said that every neuron is virtually perfused by its own blood vessel. They have an estimated surface area of around 20m2, almost half the size of a squash court and therefore, in theory, provide ample opportunity for drugs to cross from the systemic blood system to the CNS.

**Figure 1:** Blood vessel network of the human brain
However, the BBB also acts as a kind of ‘firewall’ which allows the passage of oxygen and nutrients into the CNS and brain, but also blocks the entrance of what it considers harmful or toxic molecules into the brain, and, as a consequence, it prevents the entry of >98% of the drug across the BBB pathway. This in essence is the challenge facing drug delivery across the BBB and into the CNS - the result of a natural evolution over many millennia and a barrier that is extremely efficient.

In practice there are several routes by which drugs or compounds can cross the BBB (3) (see Figure 2). The transport of macromolecules such as proteins and peptides will occur by transcytosis via the receptor mediated or adsorptive mediated pathways as they have to avoid degradation by lysosomes.

If the BBB can be crossed successfully, the drugs must then be distributed within the brain. A model for this process is proposed in Figure 3. Several challenges remain in this area, including understanding the rate of elimination versus the rate of uptake, selectivity of the distribution to the brain versus other tissue, and what dose is needed for a clinical effect. Other complicated issues that need to be well understood for any such model are half-life in plasma and what levels might cause issues or side effects in other organs in the body.
The participants described the various possible approaches to deliver drugs to the CNS or brain, both conventional and innovative, amongst which were:

- **Use of receptor technologies** – This has been investigated and has progressed over recent years now through various stages of clinical development in man. It essentially enhances drug delivery across the BBB using natural receptors at the BBB which transport a specified ligand into the brain. Molecular engineering is used to create tailor-made compounds for transport, and can for example include the use of liposomes to create nanocarriers and further PEGylation can help increase plasma half-life. This approach has proved successful as it has many advantages, including:
  - It is effective for hydrophilic and lipophilic compounds.
  - The active ingredient is not modified.
  - Drug encapsulation increases metabolic stability.
  - It can target specific receptors to enhance delivery to specific sites of action (brain).
  - It reduces off-target toxicity.
  - The carrier system can easily be labelled for identification and tracking purposes.

- **Use of implanted medical devices** – Another possible approach is the use of medical devices to help ‘open’ the BBB and allow the transport of drugs into the brain. Ultrasound, which has been used for many decades for diagnostic purposes, if emitted at specific low intensity, is known to transiently open the BBB and allow the transport of compounds. One example is the transport of chemotherapy compounds into targeted areas of the brain to treat cancerous tumors. The medical device can be inserted relatively easily, and can therefore be used for a number of targeted chemotherapy sessions while decreasing the toxic side effects of the drugs on other organs, as is the case with current chemotherapeutical approaches.

Targeting the dosing to specific regions of the brain and the relatively localized effects, a few centimeters from the source, are challenges facing these medical devices. This approach has advanced significantly in clinical studies and provides broad transient BBB opening coupled with relatively simple medical procedures which function ‘on-demand’ without anesthesia.
Nose to brain (N2B) transport – The attraction of potentially delivering drugs to the brain or CNS via the nasal cavity (see Figure 4) is based on the fact that the olfactory region within the nasal cavity (see Figure 4) is the only means of delivering drugs while avoiding the BBB. However the nasal epithelium does have some barrier properties; cells of the epithelium are connected with tight junctions so these cells are too narrow for free diffusion of macromolecules, for example (4). Some enzymatic breakdown could also occur if peptides or protein come into contact with nasal epithelium.

If drugs can be delivered to the nasal olfactory region in sufficient quantities, they could, in theory, enter the brain or CNS via the epithelium itself into the perineural space, or via sensory neurons or trigeminal nerves. It has been difficult to conclusively prove any of these above pathways for N2B delivery. Some of the challenges of using this route include ciliary clearance (a naturally occurring event), the presence of lysosomes thus limiting the use of liposomes and a risk of an allergic reaction or toxic side effects due to continuous use of the olfactory epithelium. In addition, the pH of any compounds or formulations would need to be close to the pH of the nasal mucosa to avoid irritation, and the risk of introducing pathogenic bacteria or viruses remains a difficult issue to be mitigated. In addition, the anatomy of the nose including the person-to-person variation in turbinates and the nasal septum can make it difficult to access the upper part of the nasal cavity and the olfactory region.

However several researchers and companies are reported to be making progress via this route, and if the challenges detailed above can be overcome, this could prove to be a fruitful and non-invasive approach to brain or CNS delivery for numerous therapies. Aptar (5) is working on optimizing delivery from liquid and powder nasal sprays devices to target the upper part of the nasal cavity, which is showing promise.

Several researchers and companies are reported to be making progress via the nose to brain route.

Figure 4: Nasal cavity and regions of interest for nose to brain delivery
Delivering therapies safely and efficaciously to the brain and CNS remains challenging; there is a major unmet medical need for therapies to treat a range of severe diseases and the market offers very attractive opportunities for successful future participants. It is interesting to note that many different approaches are being adopted in order to overcome the BBB and deliver drugs to the brain or CNS, and much progress has been made to date with some solutions advancing into late stage clinical studies.

Transporters are an attractive option for their ability to offer global delivery to the brain and they can be combined with the many advantages of nanoparticles. Medical devices could be precisely targeted at specific diseases such as cancer and could prove to be very effective. Alternative routes, such as nose to brain, to solve the problem could also find their rightful place in the future. Hopefully we can look forward to some of these therapies coming into mainstream use over the next few years. They will be welcomed by many patients who have no immediate or satisfactory solutions today for their CNS disorders.
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