Understanding
Brain Drug Delivery

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Revolutionising the brain

Aiswariya Chidambaram of Frost and Sullivan explains the importance of early diagnosis to tackle brain disorders such as Alzheimer’s Disease…

Although research has gone a long way in establishing an understanding of the underlying mechanism and etiology of Alzheimer’s disease since its discovery in 1906, scientists have not yet arrived at a consensus and have hypothesised a large number of disease mechanisms. This clearly reflects the lack of an effective therapy option or cure for the disease till date. Moreover, diagnosis of the disease in its initial stages still remains a challenge, as minor memory problems are mistaken for general signs and symptoms of old age. Furthermore, distinguishing the signs and symptoms of Mild Cognitive Impairment (MCI) from age-related memory loss poses a challenge in terms of diagnosis and treatment of the disease. Till date, there is no single test that can diagnose the disease with 100% certainty. The assessment of patients includes a wide variety of tests and examinations, such as medical history, mental status evaluation, and physical and laboratory examinations. Additionally, family members and physicians play a crucial role in the accurate and timely diagnosis of the disease.

Nevertheless, the high failure rates (nearly 92%) associated with Alzheimer’s disease drug compounds during clinical experimentation stages and the required enrolment of caregivers along with patients makes R&D of anti-Alzheimer’s drugs a complex, lengthy, capital-intensive and risky process.

Early Diagnosis – The Key to Timely Therapeutic Intervention

Early diagnosis of Alzheimer’s disease is critical to effectively treat patients, extend their lifespan, improve quality of their lives and consequently remove the financial and psychological burden on their families and healthcare system. Evidence suggests that the damage of brain cells of Alzheimer’s disease patients begins 10 – 15 years before the disease symptoms become prominent and noticeable. Therefore, detection and treatment of Alzheimer’s disease in its initial stages wherein drugs could provide maximum therapeutic benefits are not only likely to slow down disease progression but also potentially cure the disease. It has been estimated that a 5-year delay in the disease onset could reduce the disease prevalence as high as 50% over the next few decades. Additionally, the estimates of the Alzheimer’s Association reveal that the total annual healthcare expenditure savings incurred from such a delay could amount to over $50bn worldwide.

New Improved Diagnostic Tools

Developments in diagnostics and therapeutics of Alzheimer’s disease go hand-in-hand. The development and approval of new diagnostic tools and surrogate bio-markers over a period of time have been a boon to the Alzheimer’s disease market, facilitating early diagnosis of the disease, structured clinical trial designs and outcomes. The beta-amyloid plaques formed on the surface of the brain cells and the neurofibrillary tangles (tau protein) formed inside the brain cells are the 2 most important hallmark features of Alzheimer’s disease. Several advanced diagnostic techniques such as the cerebrospinal fluid (CSF) analysis of phosphorylated tau protein and A-beta 42 peptide, and functional neuroimaging techniques which include Single Photon Emission Computed Tomography (SPECT) imaging, fluorodeoxyglucose (FDG) imaging and amyloid Positron Emission Tomography (PET) scanning are being extensively researched in laboratories for the early and accurate diagnosis of Alzheimer’s disease and its various stages of progression. Of these, the most advanced includes GE Healthcare’s ligand based PET imaging technology, which employs the use of a radioactive tracer compound, Pittsburgh-B (PIB), a fluorescent thioflavin derivative, that binds to the beta-amyloid plaques in
patients’ brains. This method not only enables the accurate spotting of plaques, but also helps monitor the disease progression during medication.

Therefore, these advances are likely to revolutionise the industry, as it facilitates early treatment access, improves clinical trial experience significantly and enables proper market segmentation and positioning of drugs for pharmaceutical companies.

**Disease-Modifying Drugs to Revolutionize the Future Treatment Landscape**

There is no cure for Alzheimer’s disease till date. The existing conventional drug classes (acetylcholinesterase inhibitors and NMDA receptor antagonists) are only capable of alleviating memory and cognitive symptoms in patients rather than restoring lost cognitive functions or providing long-term benefits to patients. Hence, the core focus of R&D revolves around the disease-modifying drug class, which is expected to command premium pricing and fuel the growth of the Alzheimer’s disease medication market. This new drug class is expected to offer potential benefits over the conventional therapy options, as they are safer, more efficacious and aim to prevent or slow down disease progression than just improving symptoms. Furthermore, the disease-modifying drugs are expected to be increasingly used as combination/cocktail therapy with acetylcholinesterase inhibitors and memantine, thereby paving the way for additional revenue contribution from existing drugs as well.

On the basis of their mechanism of action, the disease-modifying drugs can be broadly classified into ten different classes as follows:

- It is interesting to note that the key area of focus for most of the drug developers is beta-amyloid, as the amyloid synthesis inhibitors and amyloid plaque inhibitors, together constitute nearly 37.7% of the total drug candidates in pipeline. Furthermore, the mechanism of action of nearly one third of compounds in pipeline could not be exactly identified, which reflects the complexity of the disease pathology.

Although currently there are approximately 250 disease-modifying drug candidates in pipeline, Bapineuzumab (Pfizer/Johnson & Johnson), Solanezumab (Eli Lilly) and Gammagard Liquid IV Ig (10%) (Baxter Healthcare) are the three most promising ones in phase III clinical development.

Therefore, the expected approval and launch of the first few potential disease-modifying drugs by end of 2013 are likely to triple the Alzheimer’s disease Medication Market over the subsequent 5 years until 2018.
Entering or not entering the brain – that is the answer!

“Central nervous system diseases are on their way to become as abandoned as infectious diseases, in spite of the enormous need for new treatments to reduce the suffering and the huge societal costs handling these diseases.”

Appropriate drug delivery to the brain is one of the main hurdles for treating brain diseases. Several drug industries have left the area due to too low success rates. Basic research efforts are desperately needed to understand human brain drug delivery. We have (one of) the answer(s).

The blood-brain barrier (BBB) is the most important hindering interface for drug delivery to the brain. It consists of the one cell-layer, 200 – 500 nm thin walls of the brain capillaries (1/200th of the diameter of a hair). Being 644 km in length in one human being, with a surface area of 20 m², the BBB is a very efficient organ controlling delivery of nutrients, waste products from synaptic transmission in the brain and also drug transport to and from the brain. This is achieved through many different active transport processes and through the physical presence of very tight junctions between the capillary cells.

The hindering function of the BBB is sometimes an advantage, like for the newer antihistaminic drugs for allergies, significantly reducing the sedating properties of these drugs compared to older drugs, and at the same time giving good antiallergic effects in the rest of the body. In other instances it is a huge problem when drugs intended for use in the central nervous system
(CNS) do not reach its target in high enough quantities. This is for example the case in the treatment of brain tumors. Diseases of the brain, especially with inflammatory components like Alzheimer’s disease, multiple sclerosis and others, has been shown to influence the BBB, which further complicates the disease progress, but we still do not know how drugs are handled at the BBB in disease.

According to estimations by Olesen and colleagues (Olesen et al 2003), brain disorders are accountable for 35% of all disease burdens in Europe¹. Many of the brain disorders are recognized as the greatest threats to public health as they have a neurodegenerative character and are advancing with age. Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, stroke, amyotrophic lateral sclerosis are on the top of the list of the most common neurodegenerative diseases linked to irreversible loss of brain function and development of dementia syndrome.

Currently, the majority of neurodegenerative diseases cannot be cured, prevented, or even significantly alleviated. The existing situation in the discovery and development of drugs for CNS related conditions is unprecedentedly desperate. The reasons for the apparent failure of CNS programs are summarized in Figure 1.

In early drug discovery, pharmaceutical companies struggle to identify effective candidates with the ability to enter the brain by passing the BBB. This problem in combination with a lack of relevant biomarkers and scarcity of clinically translatable animal disease models making the process of the development of CNS drugs the longest and the priciest. Contrasting the highest attrition rates make CNS drug discovery an “unprofitable” business. Therefore, many of the large drug companies have stopped or significantly reduced their CNS programs during later years (AstraZeneca, GSK, Sanofi-Aventis, Novartis, Pfizer, and Merck). CNS diseases are due to this on its way to become as abandoned as infectious diseases, in spite of the enormous need for new treatments to reduce the suffering and huge societal costs handling these diseases.

It is obvious that there are several gaps in understanding of the treatment of neurological disorders particularly related to the movement of drug from the blood to and
within the brain (Figure 2). In this regard, investigation of drug transport across the BBB has a central role. This is an issue that we have worked on for several years and to which we have initial very promising method development to contribute with to learn more about brain drug delivery.

Understanding the BBB is also a problem for the drug industry when inventing new drugs, as the BBB properties of these drugs are investigated with suboptimal methods. For evaluation of the effect of the drug on the brain function scientist has to know if the drug or drug candidate is entering the brain and if so, to what extent. Due to the presence of the BBB, blood samples cannot be used to assess the active drug content in the brain. Moreover, sampling of the brain is impossible in humans.
and can be done only in animals. Translational aspects to humans are lacking apart from a few studies \(^2\)\(^,\)\(^3\), showing that the human BBB may function differently from the rodent brain. We are therefore in desperate need of translation from animal information to humans, and from healthy situations to disease.

Understanding human brain drug delivery is like laying a puzzle backwards. The methods available are Positron Emission Tomography (PET) and sampling of the cerebrospinal fluid (CSF). While CSF sampling can comes somewhat closer to the active brain concentrations, PET measures everything that is radioactive in the brain. This includes drug that is bound to brain components and therefore inactive and metabolic waste products of the drug that are transported to the brain. By using concept and methods developed in our laboratory together with PET in humans, we can measure and dissect out the active part, which is not bound to any components of blood or brain, but is the part that is active towards the receptors \(^4\)\(^,\)\(^5\).

It is of utmost importance that financial bodies understand the urgent need for translational pharmacokinetic research from rodents to humans to disease conditions, in order to improve the treatment of diseases of the CNS, through a more optimal and knowledgeable selection of new, effective drugs for these devastating diseases. We need to understand the basis of drug transport in order to forward the field further.

References


