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SM Journal of Neurological Disorders and Stroke

Mini Review

Blood Brain Barrier Crossing for Therapeutic and Diagnostic Agents

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Article Information

Received date: Nov 09, 2016
Accepted date: Dec 19, 2016
Published date: Dec 29, 2016

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Abbreviations BBB: Blood Brain Barrier; CNS: Central Nervous System; BK: Bradykinin; NO: Nitric Oxide; SGC: Soluble guanylate cyclase; ABC cassettes: ATP binding cassettes; CRGD: Cyclic arginine-glycine-aspartic acid; DPPC: Dipalmitoyl Phosphatidylcholine; ELP: Elastin-Like Polypeptide; NRP: Receptor Neuropilin-1; BDNF: Brain Derived Neurotropic Factor; p-gp: p-Glycoprotein; LDL: Low-Density Lipoprotein; MRI: Enhance Magnetic Resonance Imaging; NPs: Nanoparticles; HAD: HIV-1 Associated Dementia; NACA: N Acetylcysteine Amide; PKC: Protein kinase; AD: Alzheimer's disease; HIR: Human insulin receptor; MAb: Monoclonal antibody; PEDF: Pigment Epithelium-Derived Factor; GDEPT: Gene-Directed Enzyme Prodrug Therapy; ADEPT: Antibody-Directed Enzyme Prodrug Therapy

Abstract

The fact that the brain is protected by the skull, the meninges and that the material which can enter is controlled by the Blood-Brain -Barrier (BBB) for bidirectional traffic is causing obstacles to the physicians in cases that remedy is needed for tumors, infections and dysfunction of the very complicated neuron cycles, billions of them, controlling all functions of life. Diagnosis is meeting great difficulties and nowadays only spectroscopy, with its latest development we can count the sound, which can give us the vague picture of what is happening inside the skull. Photo acoustic angiography is only one ultramodern way to understand the inner brain, two electrons fluorescence spectroscopy is also one of the method second to positron tomography. In all these cases, chemical agents are introduced to the sinner brain overcoming the BBB obstacle. Remedy by applying drugs is very often used either to cure tumors and infections and t5o repair neurologic dysfunction. The BBB is in all these cases a major issue to handle. In this mini review, we would like to update the reader on the confrontation with the BBB issue.

Opening words

The brain is the only organ known to have its own security system, a network of blood vessels that allows the entry of essential nutrients while blocking other substances. Unfortunately, this barrier is so effective at protecting against the passage of foreign substances that it often prevents life-saving drugs from being able to repair the injured or diseased brain [1,2].

New studies are guiding researchers toward creative ways to open this barrier and "trick" it into allowing medicines to enter. Non-polar agents can cross the blood-brain barrier far easier than polar molecules. This selectivity poses a problem if we have a polar agent that could be extremely effective in treating a disorder. However, scientists have come up with some creative solutions. Non-polar agents are lipophilic, which means they cross the blood-brain barrier by diffusing through the lipid membranes of the endothelial cells (option b in the diagram below). This accounts for the majority of Agents (also applied for pro-Drugs [3]).

Polar drug molecules, on the other hand, cross the blood-brain barrier less frequently because their charged structure makes them aversive to the lipids in the membrane of the endothelial cells. It's also difficult for them to diffuse through the tight junctions. One strategy to get around this problem is to use mannitol to remove fluids from the endothelial cells, allowing polar molecules to subsequently diffuse through the tight junctions [4]. Another method is to attach a vector to the drug, tricking the transport mechanisms on the endothelial cells to allow the polar drug through [5].

Introduction

The brain, as the central control organ on the complex multi-functional process of keeping the organism alive, control of sub-systems, thinking, memory is only a part of the complex mission that were given by the creator, is protected from the outside world by an impregnable skull made of bone materials a multilayer soft tissue barrier that permits only a few sorts of material to reach the inner parts and enable the providing of energy and nutrients for the cells, new neurons, to function. This is a nonstop operation if the organism is alive.

The Blood-Brain Barrier (BBB) is a mechanism that controls the passage of substances from the blood into the cerebrospinal fluid and thus into the brain and spinal cord. It lets essential metabolites, such as oxygen and glucose, pass from the blood to the brain and Central Nervous System (CNS) but blocks most The Blood Brain barrier is a tissue that separates the blood system nourishing the brain from the brain tissues - the neurons. It becomes a serious obstacle when drugs are to be introduced into the living brain from the blood stream [6].

The special properties of the blood-brain barrier were first observed in the late 19th century by the German bacteriologist Paul Ehrlich. He found that when he injected colored dyes into the blood stream they leaked out of capillaries in most regions of the body to stain the surrounding tissues; the brain, however, remained unstained. Molecules those are more massive than about 500 Daltons. This is a low mass in biomolecular terms and means that everything from hormones and neurotransmitters to viruses and bacteria is refused access to the brain by the BBB. It also means that

many drugs, which would other wise can treat disorders of the CNS, are denied access to the very regions where they would be effective.

Functions of the Blood-Brain Barrier (BBB)

- Protecting the brain from "foreign substances" (such as viruses and bacteria) in the blood that could injure the brain.
- Shielding the brain from hormones and neurotransmitters in the rest of the body.
- Maintaining a constant environment (homeostasis) for the brain.
- There is another way of covering the brain the meninges [There is another way of covering the brain the meninges [7,8].
- Covering the brain, the meninges and blood systems and blood brain barrier diagram.
- This tissue is complex but may become venerable to infections, cancer, and other damages like the Cerebrovascular Accident (CVA), Cerebrovascular Insult (CVI), and brain attacks. Since ancient times of mankind civilizations, in Egypt for example, physicians entered the brain by penetrating those barriers and brought remedy to the sick. One of the techniques was apparently drilling through the bone to the soft tissues of the brain.

Ancient Medicine in Neolithic Era

The Ebert papyrus is much more complete than the Edwin Smith papyrus. It is made up of 110 pages, including approximately 877 remedies. The papyrus is not based upon healing any one part of the body. It has sections that cover everything from the head to the toes to the fingers to the eyes. It also includes remedies for parasitic stomach diseases and a small section of the heart.

Crossing the Blood-Brain Barrier (BBB)

Ways to cross

There are four basic mechanisms by which solute molecules move across membranes.

- First is simple diffusion, which proceeds from high to low concentrations.
- Second is facilitated diffusion, a form of carrier-mediated endocytosis, in which solute molecules bind to specific membrane protein carriers, also from high to low concentration.
- Third is simple diffusion through an aqueous channel, formed within the membrane.
- Fourth is active transport through a protein carrier with a specific binding site that undergoes a change in affinity.

Active transport requires ATP hydrolysis and conducts movement against the concentration gradient. Movement between cells is referred to as paracellular diffusion. Paracellular transport refers to the transfer of substances across an epithelium by passing through the intercellular space between the cells [9].

The BBB has several highly selective mechanisms for transport of nutrients into the brain. Structurally, The Blood Brain Barrier (BBB) [10] is a highly selective permeability barrier that separates the circulating blood from the brain extracellular fluid in the Central Nervous System (CNS). The blood brain barrier is formed by brain

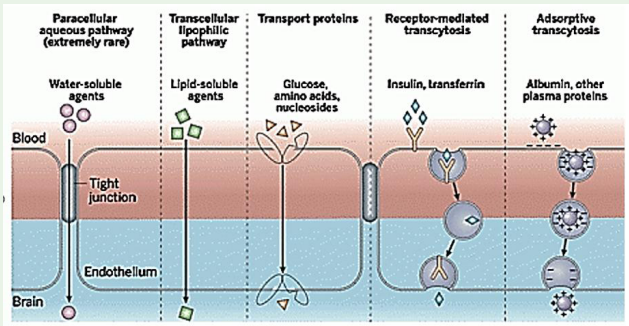


Figure 1: A schematic of various pathways crossing the BBB [9].

endothelial cells, which are connected by tight junctions. The blood brain barrier allows the passage of water, some gases, and lipid-soluble molecules by passive diffusion, as well as the selective transport of molecules such as glucose and amino acids that are crucial to neural function. Furthermore, it prevents the entry of lipophilic potential neurotoxins by way of an active transport mechanism mediated by P-glycoprotein. Astrocytes are necessary to create the blood brain barrier. A few regions in the brain, including the circum ventricular organs, do not have a blood–brain barrier.

The blood–brain barrier occurs along all capillaries and consists of tight junctions around the capillaries that do not exist in normal circulation. Endothelial cells restrict the diffusion of microscopic objects (e.g. bacteria) and large or hydrophilic molecules into the Cerebrospinal Fluid (CSF) while allowing the diffusion of small or hydrophobic molecules (O_2, CO_2, hormones). Cells of the barrier actively transport metabolic products such as glucose across the barrier with specific proteins this barrier also includes a thick basement membrane and astrocytic end feet (Figure 1).

Blood-Brain Barrier Penetration

The problem

The brain is an important organ and functions as the major command of the living organism. Therefore, it is protected from the hostile outside environment. Especially, if materials that could change the concentration of the environment of the neurons outside and inside the cell. In such circumstance the brain will lose its capabilities of mastering body functions for example. In order to deliver the cure to dysfunction of brain neurons, it is important to introduce agents into the brain. Since the BBB it is building a barrier to the blood system, -selective membranes crossings are applied used in the system for molecules to pass from the liquid blood surrounding into and out of the brain. The task is to protect brain tissue from contaminants (Agent or antibodies for example) and maintaining a liquid composition containing neurons that are very easy to change nerve conduction.

The BBB consists of capillaries nourishing the brain and lined up alongside cell lines tight tightly. This structure does not contain pores, in contrast to other capillaries membranes found in the rest of the body. In addition, and part of the unique nature of the BBB, the capillaries are covered with a fatty layer, providing compatibility with its environment. When this layer meets another oily barrier, through which the Agent will pass through the barrier. Therefore, the

entry of agents into the brain is in many cases performed by crossing through the cellular membrane of the capillaries and through For instance, Polar drugs such as penicillin cannot easily enter the brain [11,12,13,14,15]. To combat infections of the brain (meningitis is one sort), must enter in another, non-lipophilic entry. This creates the need to design drugs that work in different areas of the body, not the brain itself. So, by increasing Polar drug that does not cross the barrier in reduced side effects Central nervous. On the other hand, drugs that are designed to work in the brain, must go through design which will buy they penetrate the barrier. This is characterized by a minimum number of polar groups.

However, today many strategies are available to introduce and extract compounds into and out of the brain through this barrier.

The Main ways are

Disguise: BBB crossing strategies follow more covert means of overtaking disease in the brain sneaking through the natural pathways that already exist. Free diffusion of lipophilic molecules is one such pathway. All brain-targeting therapies currently in use employ molecules that are small enough and lipid-soluble enough to slip through the BBB in pharmacologically significant amounts. Synthesizing drugs to fulfill this condition is, of course, a means of solving the BBB problem, but it eliminates vast numbers of potentially useful polar molecules from the ranks.

A powerful tactic for taking advantage of the diffusion pathway for more general use is being developed by researchers led by Nicholas Bodor at the Center for Drug Discovery at the University of Florida. Using the "Master of Disguise" strategy, they have come up with a chemical delivery system that shepherds hydrophilic neuro peptides, which offer a wide range of potential therapeutic applications, through the BBB.

Trojan horse tactic: For therapeutic compounds that are not synthetically open to lipophilic modification or are too large for diffusion, other means of blood-to-brain entry must be explored. Attaching an active drug molecule to a vector that accesses a specific catalyzed transport mechanism creates a Trojan horse-like deception that tricks the BBB into welcoming the drug through its gates.

To fully exploit this approach will require more specialized neuroscience reconnaissance missions, particularly of the genomics and proteomics type, in order to unearth the transporter and receptor terrain of the BBB, much of which is still a mystery. However, work using the transporting systems that are already well known has demonstrated the strong promise of this method. (Because of their size and polarity), using vectors that bind to protein-specific BBB receptors. For example, Partridge's UCLA laboratory has developed what he calls "molecular Trojan horses" that deliver an array of diagnostics and therapeutics to the brain by using a peptidomimetic Monoclonal Antibody (MAb) vector that binds specifically to the rat transferrin protein receptor (Figure 2). In rat studies, they have sneaked in several important molecules, including recombinant brain derived neurotrophicneutrophic factor, which has neuro protective activity for stroke like injuries [16], and radio labeled amyloid-β for Alzheimer's diagnosis. By binding plasmid DNA-loaded liposomes to the vector, they have also successfully demonstrated non viral gene therapy delivery. Moreover, a MAb that binds to human insulin receptors has proved capable of being delivered intravenously to the primate brain [17].

Amino Acids [18] Cross the Blood-brain barrier

The BBB is hard to cross however, it was established that Brain uptake of radio labeled amino acids, amines, and hexoses arterial injection [19]. Brain capillary endothelial cells form the Blood Brain Barrier (BBB). Extensive tight junctions connect them and are polarized into luminal (blood-facing) and abluminal (brain-facing) plasma membrane domains. The polar distribution of transport proteins mediates Amino Acid (AA) homeostasis in the brain. The existence of two facilitative transporters for Neutral Amino Acids (NAAs) on both membranes provides the brain access to essential AAs. Four Na1-dependent transporters of NAA exist in the abluminal membranes of the BBB. Together these systems have the capability to actively transfer every naturally occurring NAA from the Extracellular Fluid (ECF) to endothelial cells and from there into circulation. The presence of Na1-dependent carriers on the abluminal membrane provides a mechanism by which NAA concentrations in the ECF of the brain are maintained at 10% those of the plasma. Also, present on the abluminal membrane are at least three Na1-dependent systems transporting acidic AAs (EAAT) and a Na1-dependent system transporting glutamine (N). Facilitative carriers for glutamine and glutamate are found only in the luminal membrane of the BBB. This organization promotes the net removal of acidic- and nitrogen-rich AAs from the brain and accounts for the low level of glutamate penetration into the central nervous system the luminal membrane and Na1-dependent AA transporters at the abluminal membrane may serve to modulate movement of AAs from blood to the brain. The g-glutamyl cycle is expected to generate pyroglutamate (synonymous with oxyproline) within the endothelial cells. Pyroglutamate stimulates secondary active AA transporters at the abluminal membrane, thereby reducing the net influx of AAs to the brain. It is now clear that BBB participates in the active regulation of the AA content of the brain.

The blood brain barrier extends throughout the central nervous system. Sagittal section through a mouse showing the distribution pattern of 131labeled Renografin and hydrophilic dye that does not pass the blood brain barrier 15 min after injection. All tissues take up the dye except the entire central nervous system [20]. Saturable transport of LHRH from brain to blood in mice was also determined High-performance liquid chromatography confirmed that most of the radioactivity crossing the blood-brain barrier was intact peptide.

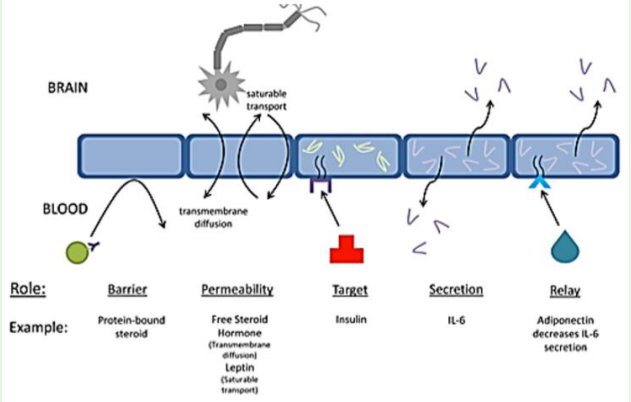


Figure 2: Photo courtesy of Professor V. Nair, Rosalind Franklin University of Medicine and Science.

The results indicate that saturable transport systems both into and out of the brain exist for I-125-LHRH [21].

Nearly every mechanism by which a substance can cross or interact with the BBB is used by one hormone or the other. In general, steroid hormones cross the BBB by transmembrane diffusion whereas thyroid hormones, peptide hormones, and regulatory proteins cross by saturable systems [22] (Figure 2).

Branched Chain Amino Acids (BCAAs) refers to three amino acids Leucine, Isoleucine, and Valine. There is a competition between aromatic AA (Tryptophan for example) and the branched amino acids. The supply of the BCAA competes with the undesired Trp which is involved in extra Serotonin synthesis in the brain. Branche Amino Acids lire AIB (alpha-amino Isobutyric acid) is applied as Trojan horse to "sneak" polar residues into the brain. AIB and alpha-(Methylamino) isobutyric acid (MeAIB) are non-metabolizable amino acids which slowly cross the blood-brain barrier but is rapidly taken up by neurons and glia via the membrane carrier system for small neutral amino acids [23]. They are transported to the brain via the transport system A [24]. One of three principal transport systems account for much of the amino acid uptake by mammalian cells [25]. AIB was found to accumulate in certain regions of the brain.

Blood volume, blood flow, and blood-to-tissue transfer of an amino acid in circum ventricular organs, such as the median eminence and sub cortical organ, and the pituitary gland of conscious rats were measured by using quantitative auto radiographic techniques and computer assisted processing of the tissue images. Retained erythrocyte and plasma volumes observed in circum ventricular organs and the anterior and neural lobes of the pituitary gland were dissimilar but in all cases, greater by several times than those in cerebral grey matter; these findings suggest the presence of a dense network of high-resistance micro vessels in circum ventricular organs. The rate of capillary blood flow in the sub cortical organ and median eminence was similar to that of grey matter, whereas blood flow in the pituitary neural lobe was several times higher than in grey matter. Thus, the apparent velocity of intra papillary blood flow is much higher in the neural lobe than in the sub cortical organ. Blood-to-tissue transfer of a small neutral amino acid, alpha-aminoisobutyric acid, was 200 to 700 times more rapid in circum ventricular organs and pituitary neural lobe than in the inferior colliculus and caudate nucleus, structures having a Blood-Brain Barrier (BBB). Morphometric analyses indicated that capillary volume and surface area were two times larger in the neural lobe than in the sub cortical organ. Moreover, capillaries of the neural lobe and sub cortical organ had numerous endothelial fenestrations and cytoplasmic pits or vesicles, whereas capillaries of the inferior colliculus had no fenestrations and fewer vesicles. These studies demonstrate quantitative differences in the microcirculatory systems not only between circumventricular organs and BBB structures but also among circumventricular organs [26].

It has been reported [27] that determinant of biological structures and has been suggested to be important in self-assembly of amyloid fibrils [28,29]. An interesting recent crystal structure of the tetra peptide Phe-Gly-Phe-Gly reveals a fully extended flat sheet conformation [30]. Peptide are of high interest for drugs aim at brain diseases, Alzheimer's Disease is in the focus, however, peptides are assumed to be a major it target for such future therapy. Therefore peptides or their surrogates are expected to advance these research efforts [31]. Since peptides in many cases are not able to cross the BBB, a vector delivery [32,33] is needed. Conjugation with monoclonal antibodies to receptors such as transferrin may be applied [34].

Fenstermacher, Goldstein published in 1978 that alpha amino isobutyric acid penetrates the BBB accumulates in certain regions of the brain [35]. Branched Chain Amino Acids (BCAAs), Leucine, Isoleucine, Valine penetrate the BBB easier than aromatic amino acids, Tryptophan [36]. Food Supplementing BCAAs prevents a serum decline in BCAAs, which occurs during exercise. A serum decline would normally cause a tryptophan influx into the brain, followed by serotonin production, which causes fatigue. 2-amino isobutyric acid has been applied in brain research [37], brain uptake data obtained from multiple-time experiments with α-amino-isobutyric acid, N-methyl-α-aminoisobutyric acid and diethylene triaminepenta acetic acid (Figure 3).

The present view of the BBB is that cerebral endothelial cells participate actively in regulating the composition of brain extracellular fluid and the Amino Acids (AA) content of the brain. The luminal and abluminal membranes work in a complementary fashion with the Na1-dependent transport of AAs occurring at the abluminal membrane, and with facilitative transport at the luminal membrane, or, in the case of Large Neutral Amino Acid (LNAAs) at both membranes [38]. Although the BBB determines the availability and therefore the brain content of essential AAs, astrocytes and neurons participate in maintaining the extracellular concentrations. Astrocytes and neurons have Na1-dependent transport systems capable of transporting NAAs and acidic AAs. These systems are actively involved in regulating AA concentrations in ECF and are especially important in the maintenance of low concentrations of neurotransmitter AAs such as glutamate, aspartate and Glycine. On the other hand, it now seems clear that the BBB also participates in the active regulation of brain ECF composition and the abluminal membrane is especially important in this role.

AIB is particularly interesting in respect to neurodegenerative diseases potential treatments. Not only that it could penetrate the BBB, it could carry with it other agents that do not cross by6 themselves, it also disrupts Ab fibrils. In this view Gazit [37] introduced D-tryptophan in connection to AIB and showed that this di peptide enters the brain through the BBB. Shatzmiller [39] applied Aib to make the polar BIBANE laser dye penetrate from the blood stream and stain the hippocampus gland with green fluorescence.

Thus methods which measure unidirectional uptake of amino acids from the blood readily demonstrate a BBB transport system for large neutral amino acids such as phenyl- alanine, leucine, tryptophan and methionine however; there is little or no transport

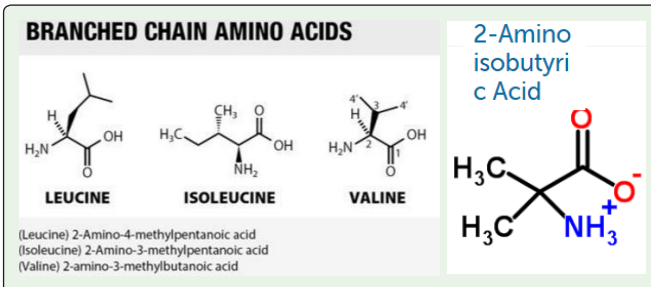


Figure 3: Branched Amino Acids.

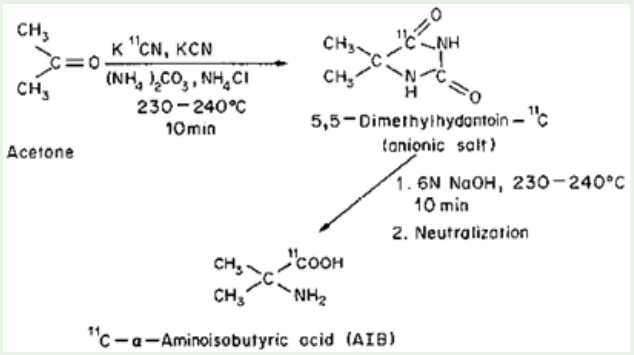


Figure 4: The preparation of [11c] α-aminoisobutyric acid ([11c] AIB) by the modified Bucherer-Strecker amino acid synthesis.

of small neutral amino acids such as Glycine, alanine, serine and pro line. These two groups of amino acids correspond respectively to the Na+-independent L system and the Na+- dependent A system for neutral amino acid transport into other cells for radio-imaging the inner brain by ^{11}C PET imaging ^{11}C AIB has been synthesized and tested (Figure 4).

The process requires about 70 min for synthesis and purification and about another 20 min to carry out the quality control procedures of which the apyrogenicit test is the limiting factor. Starting with about 1 Ci of [^{11}C] KCN, 10-20 m Ci of [^{11}C] AIB at time of [11C] AIB may be useful for amino acid transport studies *in vivo* but this application may be dependent on the specific activity of the compound. To our knowledge, there have been no reports of limitations on the specific activities of the ^{11}C-amino acids that can be produced by the Bucherer-Strecker synthesis. Therefore, if necessary, it may be possible to produce [^{11}C] AIB with specific activities greater than 0.3 ^{11}Cmmol.

Gazit has used AIB for they synthesis of a BBB penetrating dipeptide [39] (Figure 5).

The ability to cross the BBB with the aid of AIB or other carriers encouraged German scientist to look for therapy to neurodegenerative diseases in peptides and peptide mimics [40] (Figure 6).

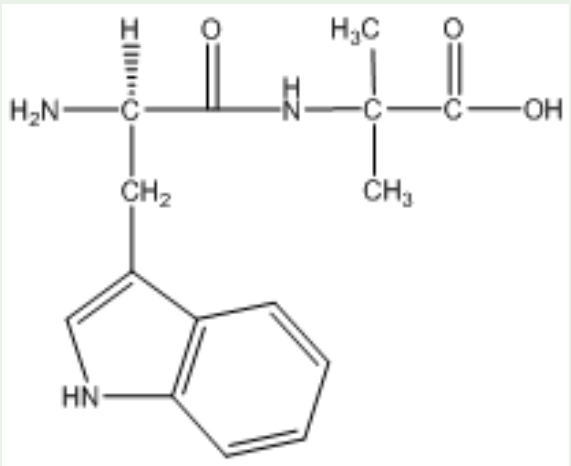


Figure 5: (R)-2-(2-amono-3-(1H-indol-3-yl) propanamido)-2methylpropanoic acid.

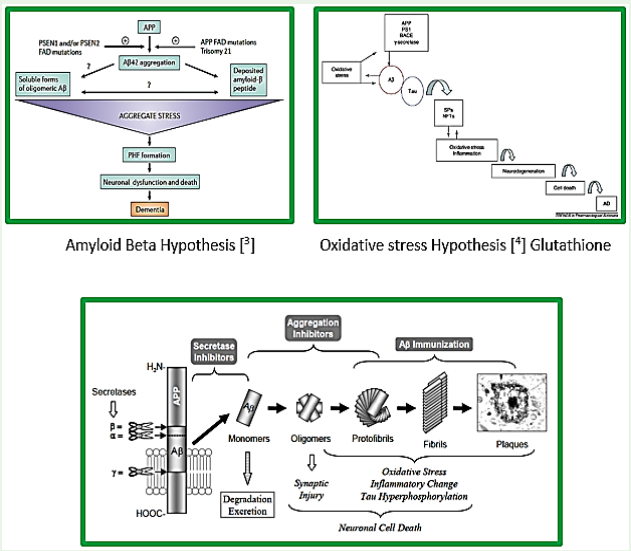


Figure 6: Amyloid beta and oxidative stress schemes.

One of the major difficulties in AD research is the diagnosis at earliest stages. Many diagnostic novel ideas are being pursued; one of them is the imaging of the inner brain focusing on the hippocampus where the dysfunction of the secretase cleavage to give the amyloid fibrils starts. Nowadays, there are two reports on agents that could be transferred to the inner living brain by injection to the blood stream [41,42]. The Korean group introcuced11C as an option for PET imaging, were as the Israeli group introduced the Bimane unit which could be transferred [45] to this, Glutathione for example in the inner brain (Figures 7 and 8).

Bidirectional flow through the BBB is essential for the functioning of the Parenchyma of the brain. While a sleep the brain excretes the "trash" Parenchyma is composed of substances formed during the metabolic function and prepares there by the organism for further proper function. The affluent is directed to the blood system and carried to the liver' kidneys where they are disposed of from the body.

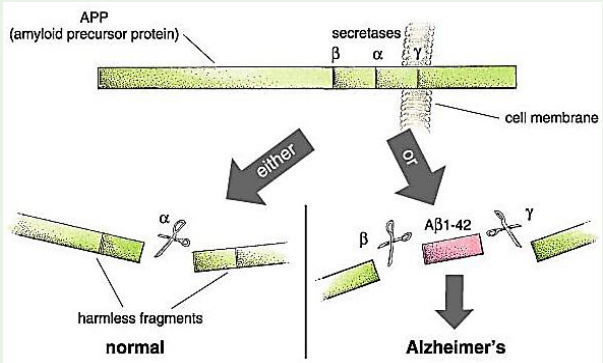
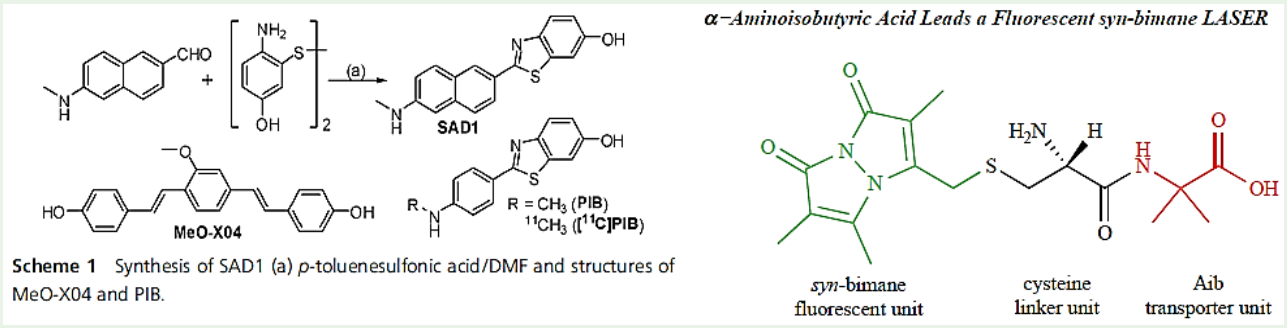


Figure 7: Secretase cuts Amyloid Precursor Protein, the turning point.

Amyloid Precursor Protein (APP) can be cut harmlessly or cleaved into Toxic frgments. When the full-length APP is cut at the α site *(left),* the resulting pieces do not harm the cell. However, when APP is cut at the *β* and γ sites *(right),* the excised fragment, known as Aβ1-42, Aggregates to form toxic plaques [43,44].



Scheme 1 Synthesis of SAD1 (a) *p*-toluenesulfonic acid/DMF and structures of MeO-X04 and PIB.

Figure 8: Blood Brain Barrier Crossing Probes [35,36].

The laboratory of Nedergaard investigated the process by two photos spectroscope and following the flux of materials to (awake mode) and from (sleep mode) the brain [46,47,48,49].

Convection Enhanced Delivery

Convection Enhanced Delivery (CED) [50] is the continuous injection under positive pressure of a fluid containing a therapeutic agent. This technique was proposed and introduced by researchers from the US National Institutes of Health (NIH) by the early 1990's to deliver drugs that would other wise not cross the blood brain barrier into the parenchyma and that would be too large to diffuse effectively over the required distances were they simply deposited into the tissue (Figure 9).

Schema of several catheters tested for convection-enhanced delivery. Arrows symbolize the flow of infuscate during convection-enhanced delivery. BTC: Balloon-tipped catheter; HFC: Hollow fiber catheter; MPC: Multiple port catheter; OPC: One port catheter; RPC: Reflux-preventing catheter.

What CED seeks to achieve is to:

i) Provide homogenous distribution of a therapeutic agent to a larger volume of brain tissue.

ii) Provide higher drug concentrations directly to the tissue.

iii) Can make use of molecules that cannot cross the Blood Brain Barrier (BBB).

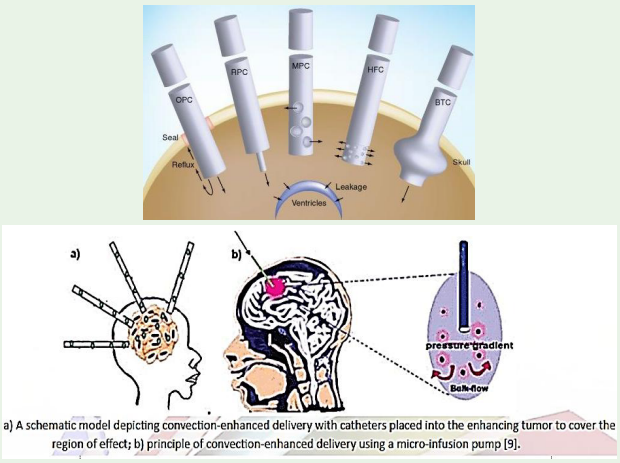


Figure 9: Convection Enhanced Delivery of a drug to the brain [50].

This treatment is more aggressive than a simple injection to the arm for example but it is applied for drugs that have to combat heavy damage to the inner brain like glioma or other malignant infections, for example.

Nanoparticles as Drug Delivery System [51]

Magnetic Nanoparticles (MNP) cross BBB: Recent studies involving coating Fe nanoparticles with an outer shell have succeeded in minimizing their oxidation and agglomeration. An effective therapeutic approach against cancer typically requires the combination of several modalities, such as chemotherapy, radiation, and hyperthermia. In this regard, the development of multifunctional nano material-based systems with combined therapeutic and molecular imaging capabilities has shown great potential but has not been fully explored. In magnetic nano materials have been at the fore-front of cancer research as noninvasive imaging probes as well as multifunctional therapeutics. Moreover, the unique physical and chemical properties of these magnetic nanostructures have enabled their wide applications in drug delivery, cancer imaging and therapy, including Magnetic Resonance Imaging (MRI) and hyperthermia (Figure 10).

Several imaging modalities are suitable for *in vivo* molecular neuro imaging, but the Blood Brain Barrier (BBB) limits their utility by preventing brain delivery of most targeted molecular probes. Reports disclose that biodegradable nanocarrier systems made up of poly (n-butyl cyanoacrylate) dextran polymers coated with polylobate 80 (PBCA nanoparticles) to deliver BBB-impermeable molecular imaging probes into the brain for targeted molecular neuro imaging. The ability to image structure and function in the brain using tools as diverse as multiphoton fluorescence imaging and Magnetic Resonance Imaging (MRI) hold the promise of providing insight into physiology and pathophysiological conditions, but are greatly limited

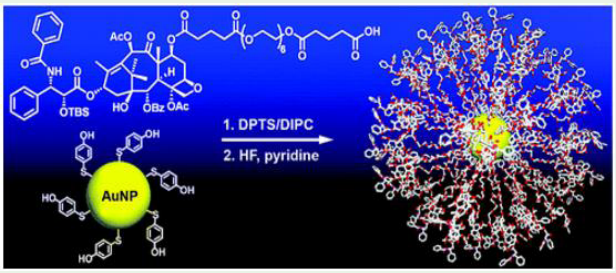


Figure 10: Nanoparticles as Drug Delivery System [51].

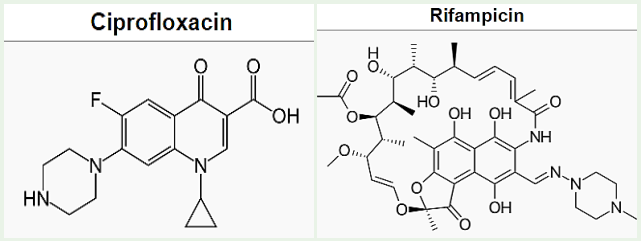


Figure 11: Antibiotics applies in brain abscess cases.

by the ability to deliver contrast agents with molecular specificity across the Blood Brain Barrier (BBB) [52]. *In vivo* effect of magnetic targeting on the extent and selectivity of nano particle accumulation in tumors of rats harboring orthotropic 9L-glio-sarcomas was quantified with MRI [53].

Strategies are becoming reality in transport of nano materials through the BBB [54]. Nanoparticles that are coated with an agent use the receptor mediated crossing of w agent to cross the BBB, Researchers at the Institute of Chemistry, Chinese Academy of Sciences in collaboration with the German investigators in ‡Institute for Biochemistry, WestfälischeWilhelms-Universität, Münster [55], that lactoferrin coated magnetic nano-particles (Fe(3)O(4)-Lf) *in vivo* animal experiments show a similar tendency but also show a clear vascular imaging ability of the Fe3O4-Lf probe during the early stage of post-injection, which strongly supports that brain delivery is achieved via the lactoferrin-receptor-mediated pathway. The current investigations further suggest that the PEG-coated nanoparticles, apart from acting as brain MRI contrast agent, can potentially be used as a brain delivery vehicle for molecules of interest for brain diseases by further coupling the magnetic particles with diagnostic, therapeutic, and/or curative effect tracking reagents using the particle surface carboxyl groups.

Brain Infections and the crossing of the blood brain barrier BBB

The adequate management of Central Nervous System (CNS) infections requires that antimicrobial agents penetrate the Blood-Brain Barrier (BBB) and achieve concentrations in the CNS adequate for eradication of the infecting pathogen [56].

Our brain, the spinal cord, and its surrounding structures can become infected by a large spectrum of germs. Bacteria and viruses are the most common offenders. Parasites, fungi, and other organisms can infect the Central Nervous System (CNS), although more rarely.

- **Location:** The infecting germ causes an inflammation of the affected area. Depending on the location of the infection, different names are given to the diseases.
- Meningitis is the inflammation of the meninges, the surrounding three-layered membranes of the brain and spinal cord, and the fluid it is bathed in, called Cerebrospinal Fluid (CSF).
- Encephalitis is an inflammation of the brain itself.
- Myelitis actually means a spinal cord inflammation.
- Abscess is an accumulation of infectious material and offending microorganisms, and this can occur anywhere within the CNS.

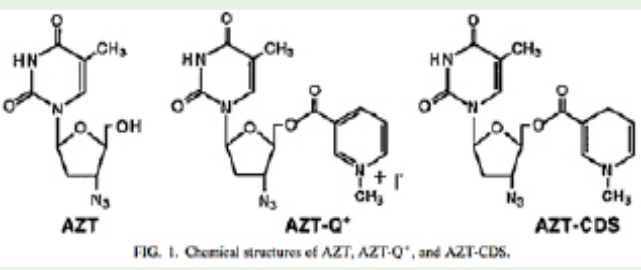


Figure 12: Antiviral pharmaceuticals designed to cross the BBB [60].

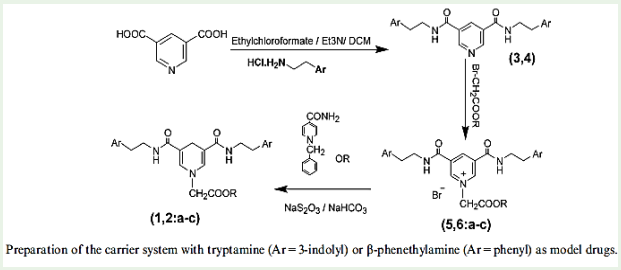


Figure 13: Preparation of Pyridinium model for BBB crossing [61].

Infections of the central nervous system include meningitis (inflammation of the cerebral or spinal meninges), encephalitis (manifestations of cerebral symptoms due to bacterial and viral invasion of the central nervous system), abscess and parasitic infections. One of the most destructive components of this disease is an encephalopathy and associated dementia spawned by direct viral infection of the brain. Antiviral agents must therefore gain access to the Central Nervous System (CNS) in therapeutically relevant concentrations if AIDS dementia.

Infection is to be adequately treated. Such pharmacokinetic considerations are often not met because of the ostensibly protective blood-brain barrier (BBB) which effectively prevents or reduces the entry of many hydrophilic drugs, including antiviral ribosides. However, there are many relatively lipophilic antibiotics but the most common antibiotics used are ampicillin, cefotaxime, ceftriaxone, gentamicin sulfate, penicillin G and vancomycin. Ciprofloxacin and rifampin (Rifampicin) are also used rifampin is often used for children (Figure 11).

Antibiotics are usually given intravenously and the dose and duration depends on several factors. Transporting therapeutics across the blood-brain barrier [57] may apply carrier systems that can cross the BBB for example privilege scaffolds like diazepine [58] through specific receptor [59]. The penetration of antimicrobial drugs as remedy for the infections is very difficult [60] since most of the anti-infective drugs do not penetrate as such through the barrier because of their physic-chemical nature (too polar for example). A Trojan horse strategy must be applied.

The connection of AZT with Dihydropyridine (DHP) was aimed to bring remedy to HIV-1 patient at early stages where the virus infects the brain (Figures 12 and 13).

DHP was also applied by Egyptian scientists to introduce model drug agent into the brain [61].

Conclusion

The penetration of the blood brain barrier is still a major task in drug design. The selection of agents by the barrier sets a high obstacle for treating dysfunction, irregularity, degeneration, tumors infections of the brain. Some strategies like disguise, Trojan-horse, drug carriers, use of receptors for agents that can carry with them other agents that by themselves are prohibited from crossing and novel techniques like nanoparticles and dendrites are applied. However, the BBB remains a good protector, alarm whistle for the medicine people, drug designers and drug producers. It is hard to cross, in some cases regarded as un penetrable. However new practical solution like Convection enhanced delivery must be applied, as an example the application of the application of some novel biosimilar drugs for brain cancer therapy. Worldwide, the incidence of primary brain tumors is on the rise. Unfortunately, noninvasive drug therapy is hampered by poor access of most drugs to the brain due to the insurmountable Blood-Brain Barrier (BBB). Nanotechnology holds great promise for noninvasive therapy of severe brain diseases. Furthermore, recent bioconjugation strategies have enabled the invasion of the BBB via tailored-designed bioconjugates either with targeting moieties or alterations in the physicochemical and/or the pharmacokinetic parameters of Central Nervous System (CNS) active pharmaceutical ingredients [62,63,64].

The introduction of Drugs into the living Brain is a major challenge. The cure of infections, tumors and viral infections is more difficult in the brain environment challenging drug delivery to become an obstacle even higher sometimes than the overcoming on the physiological dysfunction in the brain. Many approaches are examined in this respect and only a few ideas are reduced into practice. A review article by Ravi Kant Upadhyay [65] has been published in which many of the novel ideas are discussed. However, only some are followed currently as promising for the medical treatment of ill people.

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