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Commentary

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Current Approach in Medicinal Chemistry and Pharmaceutical Technology: Strategies for Drug Delivery to the Brain

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ABOUT THE STUDY

The brain is the mass of nerve tissue in the anterior end of an organism. The brain integrates sensory information and directs motor responses; in higher vertebrates it is also the centre of learning. The human brain weighs approximately 1.4 kg (3 pounds) and is made up of billions of cells called neurons. Junctions between neurons, called synapses, allow electrical and chemical messages to be transmitted from one neuron to another in the brain, a process that includes basic sensory functions and is critical to learning, memory and thought formation and other cognitive functions. The brain is the control centre of the body. It controls thoughts, memory, speech and movement. It regulates the function of many organs. When the brain is healthy, it works quickly and automatically. However, when problems do occur, the results can be devastating. Brain tumors can also press on nerves and affect brain function. Some brain diseases are genetic and we do not know what causes some brain diseases, such as Alzheimer's disease. The neurodegenerative diseases, such as Alzheimer's Disease (AD), Parkinson's Diseases (PD) and multiple sclerosis are characterized by symptoms related to movement, memory, and dementia due to the gradual loss of neurons. Brain tumors, including gliomas, astrocytomas and glioblastomas, constitute a relevant and unsolved clinical problem and the treatment of brain cancers are major challenges. Unfortunately, few safe and effective methods are known for diagnosis and treatment of Central Nerves System (CNS) disorders and this is mainly due to the anatomical characteristics of the CNS. The symptoms of brain diseases vary widely depending on the specific problem. In some cases, damage is permanent. In other cases, treatments such as surgery, medicines, or physical therapy can correct the source of the problem or improve symptoms.

Brain diseases come in different forms. Infections, trauma, stroke, seizures, and tumors are some of the major categories of brain diseases. This description provides some recent approaches for the treatment of brain pathologies

examining both medicinal chemistry and pharmaceutical technology contributions. The Blood-Brain Barrier (BBB) represents an effective obstacle for the delivery of neuro-active agents to the Central Nervous System (CNS). The presence of the BBB makes treatment of many CNS diseases difficult to achieve, because the required therapeutic agents cannot distributed in sufficient quantities across the barrier. It is estimated that more than 98% of small molecular weight drugs and 100% large molecular weight drugs (mainly peptides and proteins) developed for CNS pathology do not transmit BBB immediately. Several pharmacological chemistry and pharmaceutical technology-based strategies have been explored and developed to improve the brain penetration of potential therapeutic agents.
Medicinal chemistry-based strategies essentially target the chemical modification of low molecular weight drugs to increase their lipophilicity. It has both an analogue approach and a pro-drug approach. Only the pro-drug policy is discussed here. For instance, the formation of an inactive pro-drug is a way to increase the lipophilicity of a drug by attaching a lipophilic pro-moiety to the parent drug when it enters the CNS. Many of these examples involve ester-based pro-drugs since by appropriate esterification of molecules containing -COOH, -OH, or -SH groups, it is possible to obtain derivatives with the desired lipophilicity. The classical example of such approach is heroin (i.e., the diacetyl ester of morphine) that rapidly crosses the BBB due to its high lipophilicity. Once in the brain, it is presumed to be hydrolyzed to morphine. The same approach has been employed with other therapeutic agents such as the anticancer agent chlorambucil and the neurotransmitters dopamine and Gamma-Amino Butyric Acid (GABA).

Pharmaceutical technology-based strategies and techniques essentially represent non-invasive methods of drug delivery to the CNS and valuable approaches to enhance the transcellular permeability of therapeutic agents and bio-macromolecules throughout the BBB. They are based on the use of nanosystems (colloidal carriers), mainly liposomes and polymeric nanoparticles even though other systems such as solid lipid nanoparticles, polymeric micelles and dendrimers are also being tried. Liposomes have long been used as carrier systems for the delivery of therapeutic agents because of their easy preparation, good biocompatibility, low toxicity and commercial availability. Nanoparticles are solid colloidal particles made of polymeric materials ranging in size from 1-1000 nm. Nanoparticles are used as carrier systems in which the drug is dissolved, bound, covered, absorbed, or chemically bonded to the surface. Nanoparticles have the advantage of high drug load capacity and can provide protection against chemical and enzymatic degradation. Polymeric micelles are abruptly formed impulsively in aqueous solutions of amphiphilic block copolymers and have a core shell structure. Self-assembly occurs when the copolymer concentration reaches a threshold value known as the critical micelle concentration. The size of polymeric micelles usually varies from ca. 10 to 100 nm. The core is composed of hydrophobic polymer blocks e.g., Poly Propylene Glycol (PPG), poly D, L-lactide, poly caprolactone, etc. and a shell of hydrophilic polymer blocks e.g., PEG. Most of them are biodegradable and biocompatible. Dendrimers are highly branched polymer molecules formed by the central core to which branches are attached, the shell of the branches around the core, and the surface formed by the branch termini. They are comparable in size to polymeric micelles or nanoparticles of smaller size. Thus, for example, a typical dendrimer atom, such as a poly (amidoamine) (PAMAM) dendrimer, can have a

diameter of 1.5 to 14.5 nm. Various drugs are trapped in the dendrimer interior cavities, known as "dendritic boxes" and can release the drug after shell degeneration under physiological conditions.

CONCLUSION

Based on the study presented above, it is clear that BBB and drug delivery to the CNS is a complex and challenging task that requires close collaboration and common efforts among researchers in many scientific fields, including pharmaceutical sciences, biological chemistry, physiology and pharmacology. In this scenario, the role played by the medicinal chemists and pharmaceutical technologists is surely relevant. Medicinal chemistry-based strategies are mainly applicable to low molecular weight drugs whereas pharmaceutical technology based on the use of nano-systems. However, since the transportation systems in the BBB are relatively selective systems and dedicated to the pathway of essential nutrients and metabolism, the latter type of approach seems to have some internal limitations. A good understanding of transport mechanisms and those that modulate drug flux transporter activity and overcoming drug resistance at the BBB level is crucial.