

Advances in Nanomedicine

Chapter 1

Nanomedicine in the Treatment of Pathologies of the Central Nervous System

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1. The blood-brain barrier (BBB)

Despite its small size, just 2 kg, 3% of the corporal weight, the nervous system is one of the most complex and crucial systems of human body. It is composed by millions of neurons and glial cells that are organized in central nervous system (CNS) and peripheral nervous system (PNS). The CNS processes the sensitive information and it is responsible of sending the instructions for muscles contractions and glandular secretions. Additionally, it is behind all the thoughts, emotions and memories. The CNS structure includes two parts: the brain and the spinal cord [1, 2]. Due to its importance and its several functions, the CNS consumes big amounts of oxygen and glucose that reach the brain by means of the circulatory system. Nevertheless, the capillaries present in CNS are distinct to those present in the rest of the body, their endothelial cells are “sealed cell-to-cell” by both, tight junctions and adherent junctions, and they are surrounded by a thick layer of glial cells (astrocytes and pericytes) [1,3-6]. These characteristics (**Figure 1**) create a physical barrier between the CNS and the rest of the body, this barrier can be subdivided in three different barriers: the blood-brain barrier (BBB), which keeps the blood apart from brain tissue, the blood-cerebrospinal fluid barrier (BCSFB), which separates the blood from the CSF present in brain ventricles, and the blood-arachnoid barrier, which isolates the blood from the CSF present in the subarachnoid space (**Figure 2**) [7,8].

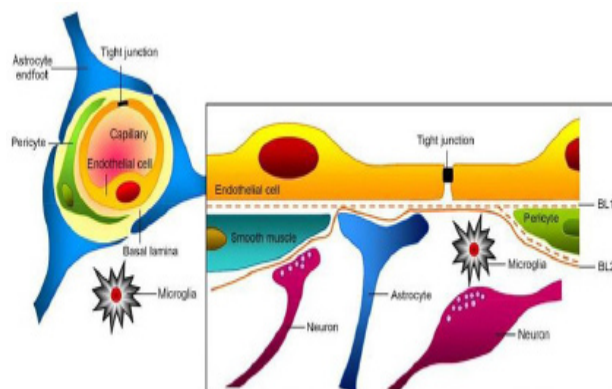


Figure 1: Scheme of the blood-brain barrier structure. Extracted from He *et al* [6].

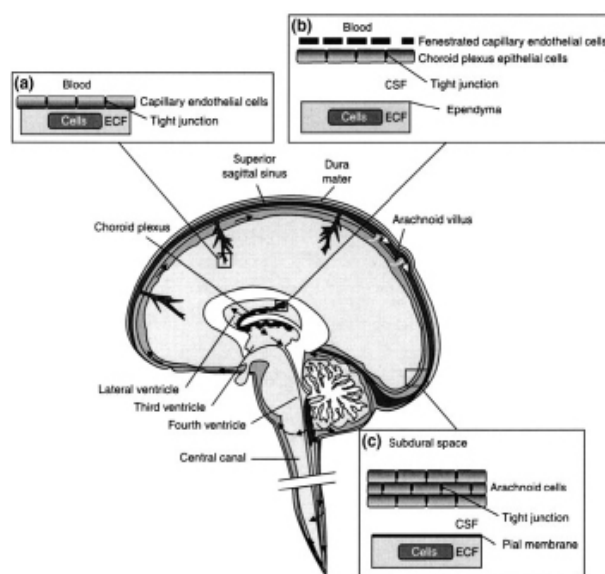


Figure 2: Brain barriers: A) The blood-brain barrier (BBB), B) The blood-cerebrospinal fluid barrier (BCSFB) and C) the blood-arachnoid barrier. Extracted from Abbot *et al* [7].

From the perspective of nutrition and transport of substances the BBB is considered the main brain barrier, as it covers the biggest part of the brain and it has the largest surface area for exchanging substances (around 150-200 cm²/g brain) [7].

In addition to the physical barrier built by the tight junctions and the glia cells, the BBB has also efflux transporters and metabolic enzymes that preserve the brain from strange substances and microorganisms. Nonetheless, these properties also hinder the delivery of drugs into the CNS when they are needed and, because of that, new strategies as nanomedicines need to be developed to overcome this barrier in case of brain disease [9].

2. Blood-brain barrier permeability

There are several routes that allow some substances to be transported through the BBB (**Figure 3**). paracellular diffusion, transcellular diffusion, carrier-mediated transport, receptor-mediated transport, adsorptive-mediated transport or cell-mediated transport [5,10–12].

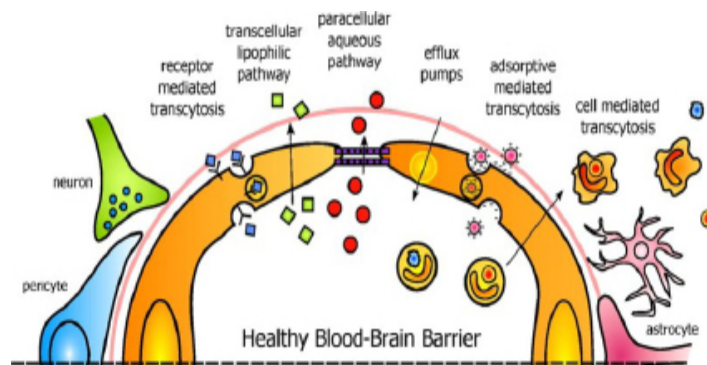


Figure 3: Transport routes across the blood–brain barrier. Modified from Chen *et al* [5].

Paracellular diffusion and transcellular diffusion are routes in which substances cross passively the BBB depending on their concentration. Concretely, paracellular diffusion is available for a very few small hydrophilic molecules (i.e. erythropoietin) that can pass between the tight junctions, although the extent of pass of this pathway is always very low. On the other hand, transcellular diffusion is only available for small lipophilic molecules, like steroids, that can be dissolved in the cytoplasm of endothelial cells and fit the following characteristics: molecular weight less than 500 Da, neutral charge, log P approximately with a value of 2 and cumulative number of hydrogen bonds less than 10.

Carrier-mediated transport is a pathway used by essential molecules as glucose or amino acids to achieve the brain. In this pathway, that requires external energy, like ATP, molecules bind to a specific transporter that by mean of changing its conformation allows their access to the endothelial cell. Some of these specific transporters are: the glucose transporter (GLUT-1) that facilitates the access of glucose to the BBB or the system L-transporters (LAT1 and LAT2) that mediate the uptake of large, neutral amino acids.

For its part, larger molecules as insulin, transferrin, lactoferrin or lipoproteins use the receptor-mediated transport mechanism for reaching the brain. In this case of active transport, a molecule bind a receptor in the surface of the endothelial cells and so both, the molecule and the receptor are invaginated into the cytoplasm of the cell. Finally, endosomes are opened and the receptor returns to the surface of the cell and the free molecule reach the brain.

In adsorptive-mediated transport, molecules are also introduced in the brain by mean of creating invaginations from cell surface. However, these molecules do not interact with any membrane receptor; they have electrostatic interactions directly with the membrane of the endothelial cells. As cell surfaces have negative charge due to their proteoglycans, this mechanism can be used by molecules that are positively charged such as albumin or other peptides.

Finally, an alternative pathway is the cell-mediated transport mechanism, also known as the “Trojan horse”. Physiologically, this route is used by immune cells to access to the brain when the BBB is not damage. Nonetheless, it is also used by pathogens that infect immune cells, as VIH, to reach the CNS.

Beside all these input mechanisms, BBB also have several efflux transporter that return molecules to the blood. Some of these transporters are: the P-glycoprotein (P-gp), some Multidrug Resistance Proteins (MRP) or the Breast cancer Resistance Protein (BCRP) [12].

3. Pathologies of the CNS

An indisputable fact is that people worldwide are living longer. Conforming to the World Health Organization (WHO): in 35 years, from 2015 to 2050, the percentage of world's population over 60 years will pass from 12% to 22%, nearly the double and, by 2020, this group of people over 60 years will exceed by far the children younger than 5 years [13].

This issue is causing an increment in the incidence and prevalence of several diseases, including pathologies of the CNS, and the main problem with these illnesses is that potentially active molecules are not able to arrive at their targets due to the BBB, making the development of new nanomedicine systems extremely necessary.

a) Glioblastoma

Glioblastoma is the most frequent and most lethal brain tumour. It comprises more than 50 % of total astrocytomas, it has an incidence of 1 per 33,330 adults per year, a median survival period of 1.16 and a 5-year survival of 2.7 %. It is formed by a mixture of altered glial cells (astrocytes and oligodendrocytes) that have acquired an extremely high capacity to invade the surrounding tissue, although extra-neural metastases are extremely rare. Normally, it progresses very quickly in just 2-3 months, unless it is developed within a pre-existing low grade astrocytoma (secondary glioblastoma) [14–17].

b) Alzheimer's disease

Alzheimer's disease is the most frequent type of dementia worldwide. It is a neurodegenerative disease, characterized by a progressive loss of memory which is caused by the accumulation of amyloid-beta peptides around the brain [14].

Just in the United States, there are approximately 5.8 millions of people who are living with dementia in 2019, 5.6 millions of people being over 65 years and 200,000 of people being younger. In fact, the 10% of people older than 65 years has Alzheimer's dementia. The incidence of this disease in USA is around 500,000 cases in 2019, but because of population aging, it is projected that by 2050, Alzheimer and other dementias in people aged 65 and older will double [18].

c) Parkinson's disease

The next most frequent neurodegenerative disease after Alzheimer's disease is Parkinson's disease which affects the substantia nigra. Parkinson's patients show a reduced level of dopamine transporters which triggers in a loss of neural functions due to the lack of dopamine available in the brain. The most characteristic symptoms of Parkinson's disease are

bradykinesia and tremors [14].

This pathology is more frequent in men than women and affects around 7-10 million of people all around the world. Its prevalence clearly increases with age, passing from 41 people per 100,000 among people who are 40 years old to 1,900 people per 100,000 when people are 80 or older. The same happens with its incidence, which grows with age until it becomes stable between people older than 80 years old [19].

d) Depression

Depression is a common mental disorder that, at global level, affects at 4.4% of the world's population. It is characterized by long duration sadness, less interest or pleasure, feelings of guilt or low self-esteem, sleeping or appetite problems, tiredness, and low concentration which can interfere with or limit one's ability to carry out major life activities. At its most severe form, depression can lead to suicide [20,21].

4. Strategies to increase the permeability through the BBB

Due to the strong opposition to the passage of substances exerted by the BBB, several strategies for increasing the amount of drug that arrives at the brain in CNS pathologies have been tried. Some of them try to use some of the transport pathways mentioned above or try to inhibit the efflux transporters, others try to momentarily modify the compact structure of the BBB and others just pass beyond the BBB by administrating the drug directly into the brain tissue or giving it intranasally [22].

Strategies that go beyond the BBB include: invasive strategies such as, intraparenchymal, intraventricular or intrathecal drug delivery strategies and non-invasive strategies like the intranasal administration. When a drug is directly delivered into the brain by injection or intracerebral implants high local drug concentrations can be rapidly achieved, but, besides their invasiveness, these methods have the disadvantages of having several side effects and being hard to control and repeat. On the other hand, intranasal administration, which profits the lack of BBB in the neural pathways connecting the nasal mucosa and the brain, is a noninvasive strategy with low risk, easy to operate and repeat, but it has a smaller drug delivery volume and big interindividual differences [6,11,22].

Alternatively, strategies that look for the delivery of drugs through the BBB try to overcome the limitations of the methodologies mentioned above. These strategies can be divided in three groups: chemical, physical and nanotechnological methods.

a) Chemical strategies

b) Physical strategies

Physical, not invasive, strategies using ultrasounds for treating pathologies of the CNS have been studied since the 1940s. However, it has not been able to use it until recently because, initially, the transfer of energy through the skull caused an extremely high overheating. [4,26]

Currently, ultrasounds strategies have been improved and they have been proved to be an alternative to temporally open the BBB. Although, there has not been proved a total lack of BBB damage when ultrasound are applied for increasing permeability through the BBB and more studies are needed to elucidate the exact mechanism by which this ultrasound waves increase the permeability [26].

At the moment, the most secure strategy for applying ultrasounds to the BBB is combining them with the intravenous administration of microbubbles, particles made of lipids or albumin and filled with gas, that makes the effect of ultrasounds to be more localized [6,22]. This method has proved to have a good selectivity of opening position, which could be an advantage over using an hyperosmolar solution or aromatic substances to open the BBB [6]. **(Figure 4)** shows a scheme of this method in which, briefly, the microbubbles are moved by the ultrasound wave near to endothelial cells and they oscillate, altering their environment and inducing mechanical stress that disrupts the tight junctions between the cells [22].

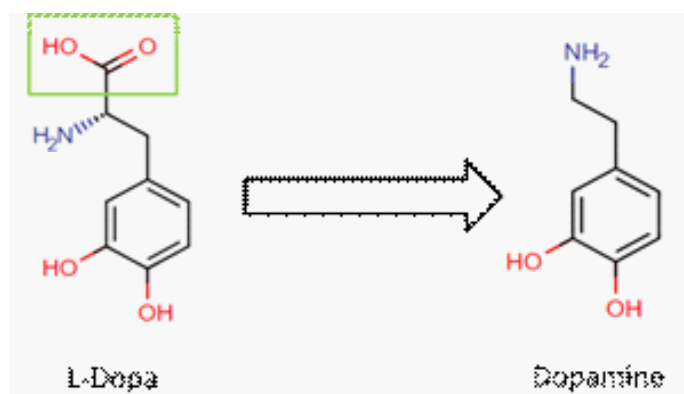


Figure 4: Scheme of the microbubble-assisted focused-ultrasound technique used for disrupting the BBB. Modified from Abdul *et al* [22].

c) Nanotechnological strategies

Nanotechnological strategies aid drugs to cross the BBB by means of the association of an unaltered therapeutic molecule with a nanoscale carrier made from lipids, polymers or metal. According to its composition, nanocarriers can be divided in 3 groups: lipid-based nanocarriers, polymer-based nanocarriers or metal-based nanocarriers [14,27]. Main types of nanocarriers that can be used as nanotechnological strategies for crossing the BBB are shown in **(Table 1)**.

Table 1. Main types of nanocarriers that can be used as nanotechnological strategies for crossing the BBB [27].

Lipid-based nanocarriers	Polymer-based nanocarriers	Metal-based nanocarriers
Liposomes	Polymeric conjugates	Magnetic nanoparticles
Solid lipid nanoparticles	Polymer nanoparticles	Non-magnetic nanoparticles
Lipid nanocapsules	Polymeric micelles	
	Dendrimers	

Nanocarriers can cross the BBB by different methods, the most important ones are: receptor-mediated and adsorption mediated transcytosis. Additionally, they can cross the barrier by paracellular diffusion when a surfactant is present in the nanocarrier and it provokes a non-permanent toxic effect in the tight junctions or the tight junctions are opened by a pathological state of the CNS. As a last method, cell-mediated transcytosis has been also used with positive results for the delivery of antiretroviral drugs in liposomes. Furthermore, the mechanisms mentioned above could be combined by the same nanocarrier for crossing the BBB [10,28,29].

Several aspects can influence the passage of nanocarriers through the BBB and they must be taken into account when they are prepared: its size, its shape, its charge and the presence of ligands.

- **Size:** For crossing the BBB through any of the transcytosis pathways, nanocarriers must be measured around or less than 50 nm [27]. Nevertheless, in studies with non-healthy animal models, carriers with a diameter below 100 nm were able to cross the BBB. Although, as the carrier becomes bigger, its BBB penetration becomes smaller [28].
- **Shape:** The most used nanocarriers for delivering drugs to the CNS are spherical nanoparticles as they are the easiest to prepare. Nonetheless, other shapes could be used with the same purpose, such as cubic particles or rod-like particles. In fact, some studies with nanorods have demonstrated promising results for this particle shape, having higher adhesion propensity and higher brain accumulations than their spherical nanoparticles counterpart [28].
- **Charge:** For effectively crossing the BBB, nanocarriers must have negative to neutral surface charge (zeta potential). Otherwise, high positive charge can damage the BBB endothelial cells [28].
- **Ligands:** Depending on the ligand added to the nanocarrier different properties can be reached. There are ligands that can adsorb proteins from the bloodstream that, then, can interplay with BBB receptors or transporters (i.e. tween 80 that adsorbs apolipoproteins). Other ligands can communicate directly with BBB receptors (transferrin receptor or insulin receptor) to promote BBB permeability. Amphiphilic peptides can actuate as ligands that increase hydrophobicity of the nanocarrier. Finally, ligands, such as PEG, can be used to increase the circulation time of the nanocarrier in the bloodstream. In all the cases, it is important taking into account the affinity between the ligand and its receptor, as a too high affinity can hinder the carrier to be released to the brain after reaching the BBB [28].

Lipid-Based Nanocarriers

Liposomes

Nanoliposomes are small vesicles constituted by lipid bilayers that can entrap both,

hydrophilic and hydrophobic drugs in its core and in its surface structure, respectively (30). Regarding the treatment of Alzheimer's disease several surface modified liposomal formulations have shown to successfully cross the BBB: stealth liposomes, transferrin modified liposomes, lactoferrin modified liposomes, glucose modified liposomes or glutathione modified liposomes [31].

Stealth liposomes are covered with PEG which rises the blood circulation time of the liposomes and prevent phagocytes from up taking them [32]. In a study carried out in mice with this type of liposomes targeted to the β amyloid plaque of Alzheimer's disease it was seen that they satisfactory increase drug concentration in brain and they were able to just bind the brain of sick mice, not the healthy ones [33].

Also, liposomes have demonstrated to be an appropriate nanocarrier in the treatment of Parkinson's disease. Recently, Qu *et al* prepared pegylated nanoliposomes loaded with a dopamine derivative N-3,4-bis(pivaloyloxy)-dopamine (BPD) and functionalized with 29 amino-acid peptide (RVG29) derived from rabies virus glycoprotein as a targeting molecule towards acetylcholine receptor on both brain capillary endothelial cells and dopaminergic cells. They saw, *in vitro* and *in vivo*, that these liposomes were able to go through the BBB and reach the substantia nigra in a better way than the free BPD. Furthermore, they saw a limited distribution to off-target organs which ensures the biosafety of the carrier [34].

Table 2: Solid lipid nanoparticles for the treatment of brain tumors.

Drug	Targeting molecule	Preparation technique	<i>In vitro</i> studies	<i>In vivo</i> studies	Reference
Camptothecin		High pressure homogenization	Porcine BCEC - Viability BCEC and RAW 264.7 - Uptake	Biodistribution in rats	(36)
Camptothecin		High shear homogenization and ultrasonication technique	A172, U251, U87, U373 glioma cell lines and THP1 macrophage cell line - Viability	Biodistribution in rats	(37)
Etoposide	5-HT moduline	Microemulsion	HBMECs - Uptake, permeability and viability		(38)
Etoposide	p-aminophenyl--D-manno-pyranoside and Folic Acid	Microemulsion	HBMECs, U87MG and HA - Viability HBMECs and U87MG - Uptake HBMECs and HA - permeability		(39)
Docetaxel Ketoconazole	Folic acid	Emulsification and solvent evaporation	bEnd.3 cells - Uptake and viability	Pharmacokinetic (plasma and brain) in rats	(40)
Docetaxel	β -Hydroxybutyric acid	Emulsification and solvent evaporation	bEnd.3 cells - Uptake and viability	Pharmacokinetic (plasma and brain) in rats	(41)

Solid lipid nanoparticles

Solid lipid nanoparticles are solid colloid drug carriers which can entrap hydrophobic drugs with a high efficiency, as they are formed by a hydrophobic solid matrix covered with a monolayer of phospholipids [35]. **Table 2** shows some examples of solid lipid nanoparticles prepared for the treatment of brain tumors, such as glioblastoma or brain metastasis. Additionally, these particles have been used to heal other pathologies of the central nervous system as depression. In 2015, Zhou and co-workers published an article in which they prepared solid lipid nanoparticles loaded with venlafaxin, an antidepressant drug substrate of the P-gp and inductor of its expression. According to their results after intravenous administration, they demonstrate that the brain uptake of venlafaxine was significantly higher when the drug was administered in the particles than when it was administered in solution, alone or combine with the empty nanoparticles or a P-gp inhibitor. Furthermore, the amount of P-gp present in the group of animals treated with the particles was the lowest one, indicating that entrapping venlafaxin in the particles prevents it from inducing the expression of P-gp [42].

Lipid nanocapsules

The last type of lipid-based nanocarrier, the lipid nanocapsules are generally constituted by a liquid oil reservoir and a polymeric protective membrane [43]. In terms of treating pathologies of the central nervous system, lipid nanocapsules functionalized with cannabidiol have been successfully prepared and tested in the human brain endothelial cell line hCMEC/D3 and in mice. Also, cannabidiol has proved to enhance the active targeting of lipid nanocapsules to glioma cells [44].

Polymeric-Based Nanocarriers

Polymeric conjugates and dendrimers

Polymer conjugates and dendrimers are both nanoscopic molecules constituted by the combination of different monomers of polymers that can be used for transporting drugs to their targets.

The main difference between dendrimers and linear polymer conjugates is their structure, while dendrimers are globular compact molecules with a regular architecture and a spherical shape, linear polymer conjugates are not compact, irregular and they have a random-coil shape. Furthermore, there are two other important differences between these nanocarriers: on the one hand, due to its preparation methodology, dendrimers are monodisperse and they have a very high structural control, whereas linear polymer conjugates are completely the opposite (polydisperse and with low structural control); on the other hand, in terms of solubility, dendrimers are highly soluble in water and linear polymer conjugates have a low solubility.

An example of dendrimer for increasing the permeability of drugs in the treatment of glioblastoma was prepared by Liu and collaborators [45]. They constructed a poly(amidoamine)

dendrimer functionalized twice with: a) angiopep-2, a peptide that can binds the less density lipoprotein receptor-related protein-1 (LRP1) on the endothelial cells of BBB provoking a receptor mediated transcytosis and b) an epidermal growth factor receptor (EGFR)-targeting peptide (EP-1) which helps the dendrimer to reach the cancer cells once it has crossed the BBB. Results showed that this strategy was effective for increasing the penetrability of doxorubicin to the central nervous system and releasing the drug in the acidic microenvironment of tumor. These facts enhanced the therapeutic efficacy of doxorubicin and limited its systemic toxicity both in *in vitro* and *in vivo* tests [45].

Dendrimers have also been tested in Alzheimer's disease, concretely, with the aim of protect synapses and memory. Poly(propylene imine) dendrimers with a histidine-maltose (G4HisMal) shell have shown to increase biocompatibility and brain accumulation after intranasal administration and to interfere with β -amyloid fibril formation *in vitro* and *in vivo*. In addition, the chronic treatment of APP/PS1 mice, Alzheimer's disease in animals, with G4HisMal protected mice from memory deterioration [46].

Polymer nanoparticles

Polymer nanoparticles can be defined as drug carrying systems formed by one or more biocompatible polymers that are not water soluble [6,11]. Some examples of these synthetic polymers are: poly(alkyl cyanoacrylates), polyethylene glycol (PEG), polylactic acid (PLA) or poly (D,L-lactide-co-glycolate) (PLGA). [6] PLA and PLGA polymers have been accepted for human use by the Food and Drug Administration (FDA) as they have proved, besides being biocompatible, to be biodegradable and not induce any inflammatory response after its administration [11].

Polymer nanoparticles can be divided in two big groups: nanocapsules or nanospheres, depending on if they have an empty core or they are solid entities and, in both cases, drugs can be loaded to the particles by adsorption to their surface or by entrapment within its matrix [6]. These particles can directly permeate the BBB, nevertheless, for obtaining a high enough transport efficiency of drugs into the brain to result in therapeutic effects, functionalization with molecules that can augment the circulation time of the particles (i.e. PEG) and stimulate their penetration into BBB endothelial cells is necessary [11].

The Na⁺-coupled carnitine transporter 2 (OCTN2) is expressed in both BBB endothelial cells and glioma cells [47,48], so it has been used as a target receptor to create new strategies for the treatment of glioblastoma. In this way, Kou and co-workers prepared PLGA nanoparticles conjugated with L-carnitine and modified with PEG (**Figure 5**). They saw, after carrying out *in vitro* and *in vivo* studies, that the particles increased anti-glioma efficacy. Furthermore, the ones with PEG1000 showed the maximum targeting efficiency and they explained that it is because it gives enough flexibility for improving the binding of L-Carnitine to its target. Also, they think that using a bigger PEG molecule provokes L-carnitine to be trapped between PEG

tails hindering its binding to OCTN2 receptor [49].

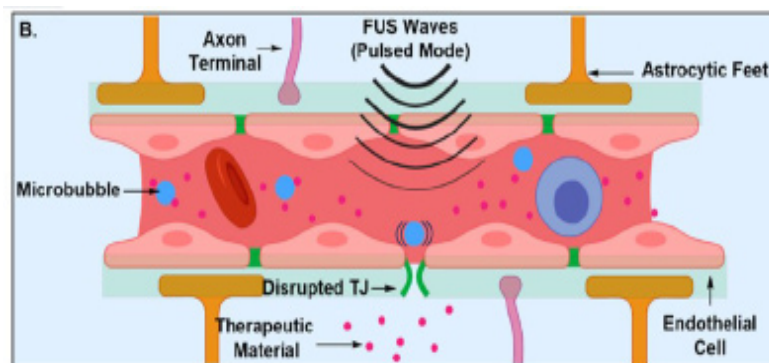


Figure 5: Scheme of the microbubble-assisted focused-ultrasound technique used for disrupting the BBB. Modified from Abdul *et al* [22].

In terms of depression treatment, plain venlafaxine-PLGA nanoparticles and venlafaxine-PLGA nanoparticles modified with transferrin or a specific peptide against transferrin receptor were prepared by Cayero-Otero and collaborators. [50] *In vitro* studies carried out with these particles in hCMEC/D3 cells showed that the highest permeability through the BBB was obtained with particles modified with a specific peptide against transferrin receptor. Nevertheless, *in vivo* tests demonstrated that, after nasal administration, the particles that reach the brain in a highest amount were the plain ones, fact that, according to the authors, would propose that, effectively, functionalized nanoparticles arrive at the brain by receptor-mediated endocytosis (taking longer) while plain NPs can quickly reach the brain by facilitated transport [50].

Polymeric micelles

A last example of polymer-based nanocarriers is polymeric micelles. They are amphiphilic particles, usually composed by a hydrophobic polymer core and a hydrophilic shell, for instance, a core of PLGA and a shell of PEG [11].

Several polymeric micelles have been studied for the treatment of cancer [51]. A study with several micelles loaded with paclitaxel shows that they were able to reduce the tumour volume more effectively than the equivalent dose of the free drug [52].

Metal-Based Nanocarriers

Magnetic nanoparticles

Magnetic nanoparticles are alternative nanocarriers for penetrating the blood-brain barrier. The most common magnetic nanoparticles are those prepared with iron oxides, such as: magnetite (Fe_3O_4), hematite ($\alpha\text{-Fe}_2\text{O}_3$), and maghemite ($\gamma\text{-Fe}_2\text{O}_3$ and $\beta\text{-Fe}_2\text{O}_3$) [53].

When a drug is carried in magnetic nanoparticles an external magnetic field, generated by a magnet, is used to generate a driving force enabling the passage of such particles from the blood to the brain [54]. Furthermore, in the case of brain tumours, as glioblastoma, once the particles have reached the tumour area, an external alternating magnetic field can be used for warming up the carriers and killing the malignant cells, without damaging too much the

healthy cells placed around it [53].

Several *in vitro* and *in vivo* tests, with small animal models, have proved the promising potential of this type of carriers, although it is important to remember that big difficulties must be overcome to be able to move these therapies to the clinical environment. One of the most important problems is to find a magnetic force strong enough for moving the particles inside the human body, as the field strength quickly decreases with target depth in the body. Moreover, there is a poor retention of the particles in the target area once the external force is removed, so new strategies for speeding up the internalization of the particles must be found [54].

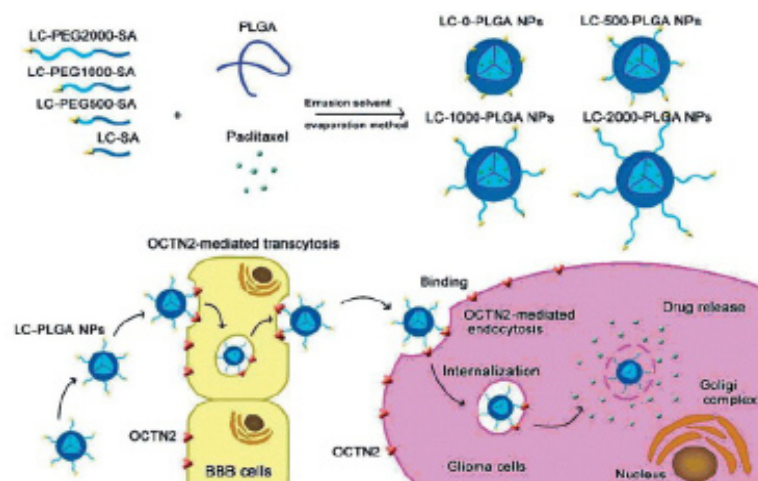


Figure 6: Scheme of the composition of L-Carnitine-conjugated nanoparticles with varied lengths of PEG spacers, and OCTN2-mediated BBB transcytosis and glioma targeting. Extracted from Kouet *al* [49].

Non-magnetic nanoparticles

Metallic non-magnetic nanoparticles, as gold nanoparticles or silver nanoparticles, have been proposed as diagnostic tools due to their extraordinary optical properties. For instance, gold nanoparticles can absorb and emit different colours depending on size, shape and aggregate status, this property is known as Localized Surface Plasmon Resonance (LSPR) [14].

Nonetheless, besides their diagnostic utility, the drug carrying and therapeutical application of non-magnetic metal-based nanoparticles have been also studied. In fact, the cell-mediated transport mechanism (“Trojan horse”), using macrophages and monocytes loaded with gold nanoparticles, has been studied for the treatment of brain tumours. After reaching the brain, when an infrared irradiation is applied, particles are warmed and they can destroy cancer cells [55].

5. Conclusions

The pathologies of the CNS are increasingly frequent due to the aging of the population and, during their treatment, health professionals usually find difficulties to cross the BBB. In fact, some molecules with adequate therapeutic activity have to be dismissed because they are not able to arrive at their therapeutic target in the CNS.

For that reason, nanotechnology opens up new possibilities for the treatment of these

pathologies. Specifically, lipid nanocarriers such as liposomes have proven useful for the treatment of Alzheimer's and Parkinson's diseases and different types of solid lipid particles have been successfully demonstrated for the treatment of brain tumours and depression. Functionalized polymer-based particles (dendrimers, nanocapsules or micelles) allow reaching cancer cells and increasing the effectiveness of antitumor treatments. Likewise, polymeric dendrimers have proven to be promising molecules in the prevention of memory loss caused by Alzheimer's disease and polymeric particles have been studied to increase the drug permeability in depression illness. On the other hand, metal-based nanocarriers have improved the quality of the diagnosis of CNS diseases as well as the efficacy of the treatment of brain tumours by reducing the impact of the side effects caused by the chemotherapy.

In that sense, nanomedicine has brought great benefits to the treatment of CNS pathologies and, since many research groups are working in this field, it is expected that the benefits of nanomedicine will soon be even greater.

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