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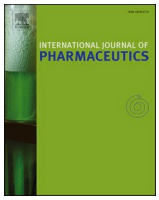

Access to the CNS: Strategies to overcome the BBB

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ABSTRACT

The blood–brain barrier (BBB) limits the access of substances to the central nervous system (CNS) which hinders the treatment of pathologies affecting the brain and the spinal cord. Nowadays, research is focus on new strategies to overcome the BBB and can treat the pathologies affecting the CNS are needed. In this review, the different strategies that allow and increase the access of substances to the CNS are analysed and extended commented, not only invasive strategies but also non-invasive ones. The invasive techniques include the direct injection into the brain parenchyma or the CSF and the therapeutic opening of the BBB, while the non-invasive techniques include the use of alternative routes of administration (nose-to-brain route), the inhibition of efflux transporters (as it is important to prevent the drug efflux from the brain and enhance the therapeutic efficiency), the chemical modification of the molecules (prodrugs and chemical drug delivery systems (CDDS)) and the use of nanocarriers. In the future, knowledge about nanocarriers to treat CNS diseases will continue to increase, but the use of other strategies such as drug repurposing or drug reprofiling, which are cheaper and less time consuming, may limit its transfer to society. The main conclusion is that the combination of different strategies may be the most interesting approach to increase the access of substances to the CNS.

1. Introduction

The central nervous system (CNS), the brain and the spinal cord, is responsible for the integration of all the sensations that peripheral nerves detect and for the coordination of responses to those sensations (Biga et al., n.d.). These responsibilities make the brain and the spinal cord the most important organs of human beings and, for this reason, they are protected by several structures: bones, meninges, cerebrospinal fluid (CSF) and blood–brain barrier (BBB) (Tortora and Derrickson, 2011a, 2011b, 2011c).

The BBB limits the access of substances to the CNS, due to the presence of tight junctions, efflux transporters, pericytes and astrocytes. Nonetheless, 6 different access routes through the BBB can be defined, as seen in Fig. 1:

- Paracellular diffusion: This term refers to the passive transport that happens between cells moving molecules from the side in which they are more concentrated to the side in which the concentration is lower. It is strictly regulated by the presence of tight junctions between the endothelial cells (Wong et al., 2013). So, only extremely small hydrophilic molecules can use this route, such as erythropoietin (Sánchez-Dengra et al., 2020). Developing new molecules able to use this route is extremely difficult, because of that, when trying to make durgs diffuse between two cells, researchers try to administer it with another substance that leaks the tight junctions, for instance, claudin-5-Binders (Hashimoto et al., 2017).
- Transcellular diffusion: Also refers to a passive transport which moves molecules from the side of the BBB with the greater concentration to the side with the lower one, but, in this case, the transport

Abbreviations: ABC, ATP-binding cassette; ApoE, Apolipoprotein-E; AUC, Area under the curve; BBB, Blood-brain barrier; BCRP, Breast cancer resistance protein; CBSA, Cationic bovine serum albumin; CDDS, Chemical drug delivery systems; Cmax, Maximum concentration; CNS, Central nervous system; CSF, Cerebrospinal fluid; ECF, Extracellular fluid; FDA, Food and Drug Administration; mAbs, Monoclonal antibodies; MRP, Multidrug resistance protein; MSNs, Mesoporous silica nanoparticles; NE, Nanoemulsion; PA, Phosphatidic acid; PAMAM, Poly-amidoamine; PCL, Polycaprolactone; PLA, Polylactic acid; PLGA, Polylactic-co-glycolic acid; Pgp, P-glycoprotein; QDs, Quantum dots; QSAR, Quantitative structure-activity relationship; SAH, Subarachnoid haemorrhage; SLNs, Solid lipid nanoparticles; SMA, Spinal muscular atrophy.

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takes place across the cells and not between them. Because of that, it is only possible for small lipophilic drugs (i.e. steroids), which meet the following characteristics: low molecular weight $\leq$ 500 Da, neutral charge, not too high or too low lipophilicity (logP $\approx$ 2) and a limited number of potential H-bonds (<10) (Teleanu et al., 2019). Normally, this way is not selected when thinking about developing a new treatment for the CNS and it is because the lipophilic drugs can get trapped inside the cell membrane (Pawar et al., 2022).

- Carrier-mediated transport: This pathway is responsible for the transport of essential molecules such as glucose and amino acids to the brain, but, any molecule similar to the glucose or to those amino acids could benefit from this route (Sánchez-Dengra et al., 2020). System L (LAT1 + 4F2hc) is a sodium-independent neutral amino acid transporter and it is one of the most important transporters involved in this route together with GLUT1. GLUT1 is a sodium-independent glucose transporter which contribute to the homeostasis of glucose and L-ascorbic acid in the CNS. Other influx transporters are responsible for the transport of monocarboxlic acids, such as lactate and pyruvate (MCT1), basic amino acids, like L-lysine and L-arginine (CAT1), nucleosides (CNT1) and organic anions and opioids (Oatp2) (Ohtsuki and Terasaki, 2007). With the aim of using this route, drugs are functionalized with the substrates of these carriers. An article published in 2022, showed how the use of the phenylalanine-phenylalanine dipeptide, substrate of LAT1 carrier, increased the retention of particles in the brain parenchyma (Alonso et al., 2022).
- Receptor-mediated transport: It is also known as receptor-mediated transcytosis and moves molecules from one side of the BBB to the other using vesicles that are formed after they join a specific receptor. This is the case for big macromolecules such as insulin, transferrin or lipoproteins (Pulgar, 2019; Sánchez-Dengra et al., 2020). In one of the latest articles where the transferrin receptor is used to improve the treatment of glioblastoma, self-assembling exosomes are prepared, which are able to join free transferrin while circulating in the bloodstream and, thus, they access to the CNS (Cui et al., 2023).
- Adsorptive-mediated transport: This pathway conforms a non-specific way of transcytosis which can be used by polycationic substances, such as albumin or other peptides, which, after interacting with the negative surface of endothelial cells, are embedded into vesicles (Sánchez-Dengra et al., 2020).
- Cell-mediated transport: Finally, in this route, cells, normally from the immune system, move directly across the BBB by means of transcytosis. In some cases, as in virus infections, these cells are used as "trojan horses" to introduce molecules into the brain (Sánchez-Dengra et al., 2020). A comprehensive review published in December 2022, analysed the use of neutrophils as "trojan horses" for the treatment of glioblastoma. This type of cells can be loaded with nanocarriers previous to administration or nanocarriers can be designed to be specifically taken up by neutrophils. It has been observed that, this technology can prevent tumor recurrence in glioblastoma and lead to the complete recovery in animal models (Hosseinalizadeh et al., 2022).

In addition to those 6 routes, which would allow molecules to reach the brain or the spinal cord, the BBB has several efflux transporters whose mission is to expel from the CNS those toxic or potentially dangerous substances that manage to reach it and to remove the metabolic products from the brain. Some examples of efflux transporters present in the BBB are the ATP-binding cassette (ABC) transporters: P-glycoprotein (Pgp - MDR1), the multidrug resistance protein (MRP) family and the breast cancer resistance protein (BCRP) (Löscher and Potschka, 2005a). Pgp was first detected in endothelial cells of human BBB in 1989 and since then several studies to evaluate its function and location have been carried out. In fact, it is the most studied efflux transporter of the BBB. It has been seen that, in mammals, Pgp can be found in the apical side of endothelial cells, so those molecules that enter these cells are directly pushed back to the blood. Furthermore, Pgp has also been detected in parenchymal and perivascular astrocytes and in neurons, especially when the animal models suffer seizures (Löscher and Potschka, 2005a; Volk et al., 2004, 2005).

All the pathologies that affect the CNS, with the exception of meningitis, have increased their global prevalence in the last two decades. Specifically, from 2000 to 2019, the prevalence of brain and CNS cancers has increased by 46%, the prevalence of stroke by 36%, neurological disorders by 24%, mental disorders by 20%, substance disorders by 17% and encephalitis by 2%. This fact makes necessary the development of new treatments to combat them. Nonetheless, about 85% of CNS trials fail (WCG Institute, n.d.) and, in some cases, it is because the new molecule cannot cross the BBB, problem that can be can be tackled with different strategies.

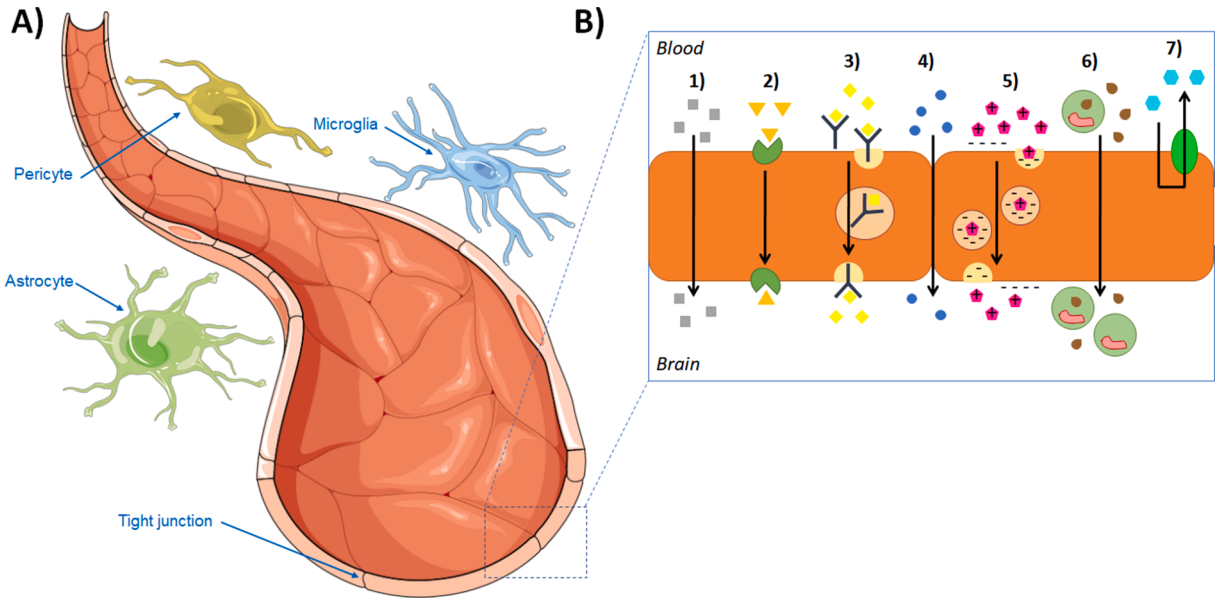

Fig. 1. Scheme of the BBB structure **(A)** and the different mechanisms of transport that can be found on it **(B)**: (**1**) Transcellular diffusion, (**2**) Carrier-mediated transport, (**3**) Receptor-mediated transport, (**4**) Paracellular diffusion, (**5**) Adsorptive-mediated transport, (**6**) Cell-mediated transport and (**7**) Efflux transport. Vectors downloaded from Servier Medical Art ("SMART - Servier Medical ART," n.d.).

2. Strategies to increase and allow the access of substances to the CNS

When trying to overcome the BBB, several strategies can be attempted which can be divided in: invasive strategies and non-invasive strategies. The invasive techniques include the direct injection into the brain parenchyma or the CSF and the therapeutic opening of the BBB, while the non-invasive techniques include the use of alternative routes of administration (nose-to-brain route), the inhibition of efflux transporters, the chemical modification of the molecules (prodrugs and chemical drug delivery systems (CDDS)) and the use of nanocarriers (Passeleu-Le Bourdonnec et al., 2013; Sánchez-Dengra et al., 2020).

2.1. Invasive strategies

Invasive strategies tend to be the least used ones because of the inconveniences and discomfort that they cause to the patient. Nonetheless, in some pathologies they are the only feasible option.

2.1.1. Direct injection

The direct injection of drugs or the implantation of controlled release systems into the brain parenchyma have been studied for the treatment of different pathologies: cancers, stroke, neurological disorders or mental disorders (Kaurav and Kapoor, 2017). The implantation of controlled release systems requires the opening of the skull, but allows long-term treatments, as drugs can be released during even several months (Bors and Erdő, 2019). In the following bullet point list, some examples of brain implants studied in different diseases are summarized:

- Glioblastoma: In 1996, the FDA approved a carmustine implant (Gliadel® wafer) for the treatment of glioblastoma. Currently, it is indicated for the treatment of recurrent glioblastoma and newly-diagnosed high-grade glioma as an adjunct to surgery and radiation. It has the advantage that it can be implanted during the same surgery in which the tumor is resected and it helps to eliminate the tumor cells that are not removed during the surgery, avoiding the adverse effects of a systemic administration of carmustine (Arbor Pharmaceuticals LLC, 2021). Studies have proved that carmustine is released by diffusion during several days and significant levels of drug can be measured within 5 cm of the implant for 30 days after implantation. Besides that, these implants are able to increase the survival rate of glioblastoma patients by 2–3 months, as it was observed in a couple of phase III reports (Study 1: median survival = 13.9 months.vs. 11.6 months, implant.vs. placebo; $p = 0.03$ and study 2: median survival = 13.8 months.vs. 11.6 months, implant.vs. placebo; $p = 0.017$) (Bota et al., 2007; Kaurav and Kapoor, 2017). In addition, according to a post-marketing study carried out in Japan, the risk of toxicity with the wafers is tolerable as, only 35.7% of the patients studied suffered adverse effects (22.2% cerebral edema, 9.9% convulsions, 4.8% impaired healing and 3.4% infection) (Nishikawa et al., 2021).
- Epilepsy: The direct injection of antiepileptic drugs to the seizure focus has proved to be well tolerated and effective in terms of anticonvulsant activity in several animal studies (Gernert and Feja, 2020; Kaurav and Kapoor, 2017). For instance, the direct injection of phenytoin into the cortical focus of an epilepsy animal model was able to control the seizures better than a systemic administration of a higher dose of the same drug (Gernert and Feja, 2020). More sophisticated devices which are able to measure the electrical activity of the brain and release drug according to this activity have also been proposed for the management of epilepsy (Kaurav and Kapoor, 2017). The device proposed in 2012 by Salam *et al.* was able to release drug just 16 s after the beginning of the electographical detection of a seizure onset (Salam et al., 2012).
- Schizophrenia: A long-term (5 months) delivery system has been also tested for the treatment of schizophrenia in animal models (Kaurav and Kapoor, 2017; Siegel et al., 2002). The reason for studying this kind of systems is that they would improve patient autonomy as they solve the problem of lack of adherence to the treatment normally associated to mental disorders (Siegel, 2002).
- Stroke: Solid implants to prevent neurological damage after stroke have been studied during years (Kaurav and Kapoor, 2017). For instance, since 1999, nicardipine prolonged-release implants have been tested with success for the prevention of vasospasm in patients with subarachnoid hemorrhage (SAH) (Krischek et al., 2007). In fact, nowadays, we can find a phase 2 clinical trial, that is currently recruiting participants, in which rod-shaped implants loaded with 4 mg of nicardipine (NicaPlant®) will be administered to patients with SAH to test if they are able to reduce neurological complications associated to this pathology.

On the other hand, the direct injection into the CSF is more accessible, but it is not really efficient because of the lack of diffusion between CSF and ECF (Passeleu-Le Bourdonnec et al., 2013). Furthermore, it must be considered that only if the drug is injected into the ventricles, it will be distributed in the whole CSF. Nonetheless, this type of injection is indicated in some infectious diseases, such as meningitis (Nau et al., 2010).

2.1.2. Therapeutic opening of the BBB

The other invasive technique that can be used to increase the access of substances to the CNS is the therapeutic opening of the tight junctions in the BBB, which can be obtained by either administering hyperosmolar solutions or using ultrasounds (Sánchez-Dengra et al., 2020).

The administration of hyperosmolar solutions typically prepared with mannitol or other aromatic substances makes endothelial cells to release water and reduce their size, resulting in an increase in the space between them (Passeleu-Le Bourdonnec et al., 2013). This type of treatment is only used for treating life-threatening diseases, as the shrinkage of endothelial cells derives in a non-selective opening of the BBB and both, drugs and toxic substances, could reach the CNS provoking neurological complications (aphasia and hemiparesis) (He et al., 2018). In addition to that, the administration of mannitol with several penetration markers has shown that the mannitol derived BBB disruption is not homogenously distributed and different permeability rates can be detected depending on the region of the brain analysed (Brown et al., 2004).

A more selective opening of the BBB can be obtained by means of combining the use of ultrasounds with the administration of microbubbles (small particles of 1–10 μm which contain heavy gases). When using this technique, microbubbles are directed towards a specific area of the brain, moving them with ultrasounds, and once in the correct place they interact with the endothelial cells and disrupt the tight junctions, leaving a free way for drugs to access the BBB (Sánchez-Dengra et al., 2020). Besides that, microbubbles can also be loaded or externally modified to carry some drugs on them. This technique has the advantage of safely opening just a desired area of the BBB without requiring a high ultrasound energy (Bors and Erdő, 2019).

The combination of ultrasounds and microbubbles has been used to improve the access of monoclonal antibodies (mAbs) to the CNS, with the aim of targeting a specific point and calling the immune system to attack it. Several mAbs in combination with this strategy have proved their efficacy in the treatment of brain cancer and neurodegenerative disorders (Fishman and Fischell, 2021; Janowicz et al., 2019; Mainprize et al., 2019; Song et al., 2018).

2.2. Non-invasive strategies

As said before, the non-invasive strategies to increase the access of substances to the CNS include the nose-to-brain route of administration, the inhibition of efflux transporters, the development of prodrugs and CDDS and the use of nanocarriers (Passeleu-Le Bourdonnec et al., 2013;

Sánchez-Dengra et al., 2020).

2.2.1. Nose-to-brain route

The olfactory area of the nasal cavity can be used as an alternative route for the delivery of molecules to the CNS. It is not clearly defined how drugs can reach the brain by means of this route, but what is clear is that olfactory nerves connect directly the nasal cavity with the CNS without having any BBB around them. It is thought that drugs administered into the nasal cavity can use two different pathways to travel until the brain: (a) the olfactory nerves transportation or (b) the trigeminal nerves transportation. The second one can only happen after the drug has been absorbed from nasal mucosa (Wang et al., 2019). The main advantages and limitations of this route of administration are summarized in Table 1.

For example, the intranasal administration of insulin has been considered a promising option for the treatment of Alzheimer's disease. In fact, several studies have proved that after administering insulin via intranasal, it can be detected in CSF and not in plasma and it can improve the cognitive response of Alzheimer's disease patients (Freiherr et al., 2013; Wang et al., 2019). Nonetheless, a recent clinical trial with 289 patients concludes that no cognitive or functional benefits of intranasal insulin administration could be observed after 12 months and it proposes that more efforts need to be done in the development of intranasal delivery devices (Craft et al., 2020).

Migraine is another pathology in which intranasal administration has been deeply studied (Chi et al., 2019; Dodick et al., 2005; Logemann and Rankin, 2000; Menshawy et al., 2018; Rapoport et al., 2004). The last device approved by FDA for the treatment of this pathology, Trudhesa®, was allowed to be commercialized in the USA in September 2021. This product contains dihydroergotamine mesylate, a well-known anti-migraine drug, that is directly delivered to the upper part of the nasal cavity. A phase 3, open-label safety study has shown that pain can start disappearing just 15 min after administration and relief can last 2 days after just one dose (Drugs.com, 2021; NeuroPharma®, 2021).

2.2.2. Inhibition of efflux transporters

As already said, efflux transporters such as Pgp, MRP family and BCRP, are responsible for expelling potentially toxic substances and metabolic products from the CNS. Because of that, when the drug of choice is a substrate of this type of transporter, they hinder the treatment of pathologies affecting the brain or the spinal cord. The coadministration of the drug in question with an inhibitor of the efflux transporter for which it is substrate is another strategy for overcoming the BBB, but it must be used with care as the inhibition of efflux transporters can lead to the massive entrance of xenobiotics to the CNS and, subsequent, unwanted side effects (Bors and Erdő, 2019; Passeleu-Le Bourdonnec et al., 2013).

Industries have worked in the development of efflux transporters during several years, specially, in the development of inhibitors for Pgp, for which three generations of molecules can be distinguished (Löscher and Potschka, 2005b):

- 1st generation: This generation of Pgp inhibitors includes several molecules, i.e. verapamil, quinidine or cyclosporin A, which, having been developed for the treatment of different pathologies, showed to have some cytotoxicity as they competed for the efflux transporter with other molecules. Nonetheless, these molecules, which were not specifically designed for inhibiting Pgp and have low affinity for it, can interact with other transporters and enzymes provoking unexpected adverse effects and need a too higher dose to induce a proper inhibition of the efflux transporter (Palmeira et al., 2012).
- 2nd generation: Trying to reduce the pharmacological effect and increase the inhibition power of the molecules from first generation, several chemical modifications were performed to the original drugs. Following this basis, dexverapamil, the R-enantiomer of verapamil, or valspodar, derivative of cyclosporin A, were discovered. However, the inhibitors from this second generation are not selective of Pgp and interact with metabolic enzymes, causing undesirable adverse effects. This is the case of valspodar which competes with other molecules for cytochrome P450 leading to an increase in the concentration of other xenobiotics (Palmeira et al., 2012).
- 3rd generation: Finally, in this last generation, new molecules, such as zosuquidar, tariquidar or laniquidar, have been directly designed making use of computational tools and quantitative structure–activity relationships (QSARs). So, they are able to specifically inhibit Pgp without interacting with other transporters or metabolic enzymes. Nevertheless, not everything is ideal, as some unexpected adverse effects have been observed when testing these molecules in clinical trials (Palmeira et al., 2012).

HIV can reach the brain using the infected immune cells as "trojan horses" to cross the BBB. Once there, the virus can multiply and use the CNS as a reservoir, as the drugs designed for their elimination fail to cross this barrier (Osborne et al., 2020). In this regard, the use of Pgp inhibitors have proved to be effective in the treatment of HIV CNS infections (Passeleu-Le Bourdonnec et al., 2013). In 2017, Namanja-Magliano *et al.* developed a homodimer of azidothymidine, an antiretroviral drug also known as zidovudine, which was able to inhibit both, the Pgp and the ABCG2 efflux transporter. Researchers concluded that this type of homodimer has potential to enhance the delivery of antiretrovirals across the BBB, as they block two transporters at the same time allowing the free drug to stay in the brain (Namanja-Magliano et al., 2017). However, extra research needs to be done, as if the studies carried out with this homodimer are looked for it can be seen that only in vitro information can be found.

2.2.3. Chemical strategies: Prodrugs and chemical drug delivery systems (CDDS)

The chemical modification of molecules is a strategy that has been used not only for obtaining more powerful inhibitors of the efflux transporters present in the BBB, but also for obtaining new drug candidates with more chances to cross this barrier.

On the one hand, the development of prodrugs consists in the chemical modification of an active molecule with the aim of increasing its lipophilicity. Once it has crossed the BBB, the prodrug loses its "extra" portion and becomes an active molecule ready to perform its mission. When talking about prodrugs for the treatment of pathologies affecting the CNS, the typical example is L-Dopa, an inactive prodrug of dopamine used in the treatment of Parkinson's disease (Passeleu-Le Bourdonnec et al., 2013; Sánchez-Dengra et al., 2020).

On the other hand, when a chemical modification is used for

Table 1
Summary of the main advantages and limitations of the nasal route of administration for the treatment of pathologies affecting the CNS (Veronesi et al., 2020; Wang et al., 2019).

	Advantages
1	Avoidance of plasma exposure, peripheral metabolism and peripheral side-effects, as the amount of drug that can reach general circulation through the nasal vasculature is depreciable (bioavailability = 0.01% − 0.1%).
2	Reduced risk of infection due to the lack of invasiveness of the administration technique.
3	Ease of administration for the patient, because drugs can be formulated in nasal sprays.
	Limitations
1	Only a small volume (100–250 μL) and a small amount of powder (20–50 mg) can be directly administered to the nasal cavity. So, this route is only feasible for very potent drugs which do not need high doses.
2	Enzymes present in nasal mucosa may metabolize the drugs administered into nasal cavity.
3	Drugs and formulations designed to be administered by this route should not irritate the nasal cavity.
4	The presence of an upper respiratory infection may alter the nasal environment and hinder the drug delivery to the brain.

appending a bioremovable targeting structure to a drug, then, a chemical drug delivery system (CDDS) is obtained (Sánchez-Dengra et al., 2020). The route for obtaining the active drug from a CDDS is more complex than when using prodrugs, which allows researchers to obtain intermediary molecules that once cross the BBB are trapped in brain parenchyma where they are not active yet but where they can be accumulated, this is known as the "lock-in" strategy (Grabrucker et al., 2013; He et al., 2018). For instance, linking dihydrotrigonelline to a drug forms a CDDS which works in three phases (Rautio et al., 2008), as shown in Fig. 2:

1. Dihydrotrigonelline increases the lipophilicty of the drug enabling it to cross the BBB.
2. When the CDDS crosses the BBB it is oxidized and a positively charge molecule is obtained. The positive charge prevents the intermediary molecule from crossing the BBB back to plasma.
3. Finally, esterases hydrolyse the intermediate molecule and slowly release the active drug.

First CDDSs are quite old. In fact, we can find a study from 1989 in which dihydropyridine is attached to some penicillinase-resistant penicillins to increase their BBB permeability. Researchers made biodistribution tests in rat and rabbit and they observed that all the penicillins (methicillin, oxacillin, cloxacillin, and dicloxacillin) were detectable in the CNS after the chemical modification, but none of them were detected when administered as they were (Pop et al., 1989).

2.2.4. Nanocarriers

The use of nanocarriers, small particles ranging from 1 to 100 nm, has proved to facilitate the delivery of drugs to the CNS. It is because they are able to protect the drug from enzymatic degradation and they can improve plasma stability and solubility. Furthermore, they can be designed to be directed towards a specific targeting, thus, minimizing non-desired side effects (Ahlawat et al., 2020). Nonetheless, it is important to remark that for all this to happen the nanocarrier must not release its content prematurely, so, the ideal nanocarriers for CNS delivery have: (A) two different ligands, a first one which contributes to BBB passage and a second one, whose aim is to target the carrier to a specific area of the brain and (B) a responsive (pH or enzymatic triggered) system which quickly releases the drug once it has reached its target but prevents it from leaving the carrier while it is on its way to it (Alexander et al., 2019).

2.2.4.1. Liposomes. Liposomes a are small vesicles, first discovered in the 1960 s, formed by a phospholipid bilayer which entraps a small volume of aqueous phase inside them. Because of that, they can incorporate both lipophilic drugs, among the lipids of the bilayer, and hydrophilic drugs, on the inside core (Passeleu-Le Bourdonnec et al., 2013; Vieira and Gamarra, 2016). Depending on their complexity, liposomes can be classified in three different generations:

- 1st generation: These are the simplest model of liposomes. They are constituted just by the lipid bilayer and, because of that, they tend to aggregate and be eliminated by the reticuloendothelial system (Passeleu-Le Bourdonnec et al., 2013).
- 2nd generation: In this second group, the phospholipid bilayer is surrounded by polyethylene glycol, which makes liposomes less recognisable as foreign bodies and increases their stability. Liposomes from this group are also known as stealth liposomes (Passeleu-Le Bourdonnec et al., 2013).
- 3rd generation: The most complex liposomes are included in this group. They are PEGylated like in the 2nd generation, but they also have other moieties linked around them which help in targeting (Passeleu-Le Bourdonnec et al., 2013).

Liposomes from third generation have been widely studied for the treatment of different pathologies affecting to the CNS (Vieira and Gamarra, 2016). For instance, multifunctionalized liposomes, with apolipoprotein-E (ApoE) and phosphatidic acid (PA), have been tested for the treatment of Alzheimer's disease. ApoE acts as a first ligand helping the particle to cross the BBB and PA targets the liposome towards β-amyloid plaques and is able to break them (Agrawal et al., 2017; Bana et al., 2014; Ross et al., 2018). In vitro tests with hCMEC/D3 monolayers show an increase in BBB permeability after the functionalization of PA-liposomes with ApoE. This increase in permeability was confirmed later on with a biodistribuiton assay in healthy mice in which researchers observed that after 24 h the brain/blood ratio was 5-fold higher with dual liposomes than with PA ones (Bana et al., 2014).

On the other hand, in 2019, Xiao et al. designed ascorbic acid-thiamine disulfide system liposomes loaded with docetaxel which may be an interesting tool for the treatment of glioblastoma. These liposomes followed a "lock-in" behaviour similar to that presented above when talking about CDDS: once the liposomes cross the BBB, the thiamine disulphide system is reduced gaining a positive charge which entrap them in the brain. The pharmacokinectic parameters obtained after the administration of the liposomes and free docetaxel to adult mice show a 3.24-fold and a 5.61-fold increase in the area under the curve (AUC) and the maximum concentration (Cmax) in the brain (Xiao et al., 2019).

2.2.4.2. Solid lipid nanoparticles. Solid lipid nanoparticles (SLNs) are constituted by a matrix of lipids, because of that they are useful for the delivery of hydrophobic drugs (Sánchez-Dengra et al., 2020). In 2019,

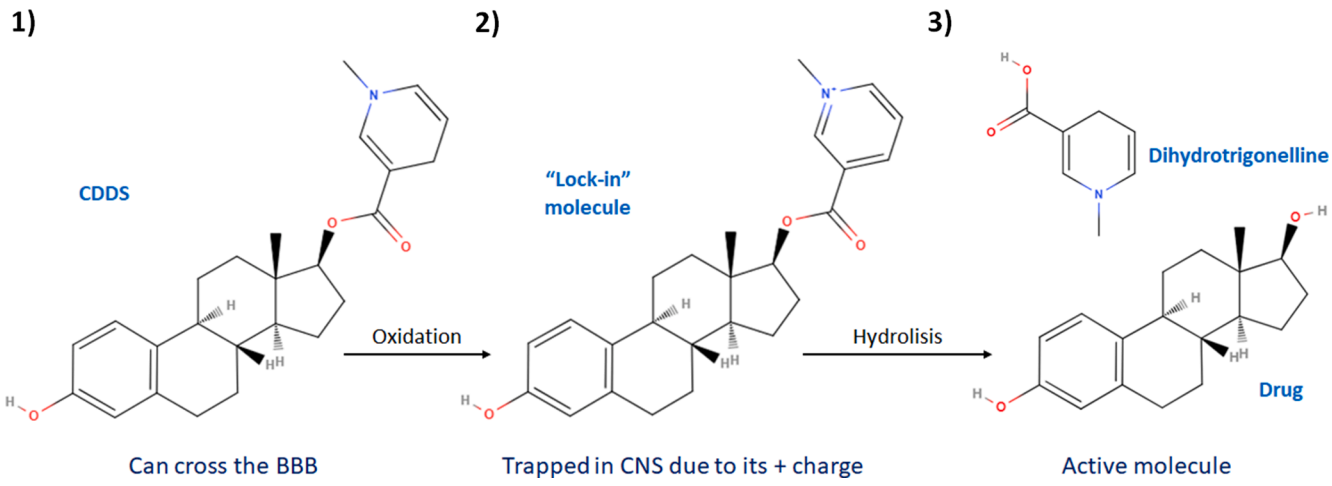

Fig. 2. Mechanism of action of a dihydrotrigonelline CDDS.

He *et al.* studied SLNs, composed of glyceryl monostearate and glycerol tristearate and loaded with β-elemene, for the treatment of glioblastoma. β-elemene is a natural essential oil with anti-tumor activity. The SLNs loaded with this drug proved to reach a greater concentration in plasma and in the brain, both in mice and rats, which would propose this formulation to improve BBB permeability of β-elemene (He et al., 2019).

The previous study together with others in which plain SLNs are administered in vivo prove that this type of nanocarrier can inherently increase the penetration of drugs across the BBB (Lombardo et al., 2020). Nonetheless, in other studies the SLNs have been functionalized and they have obtained very promising results too, for instance:

- SLNs loaded with quinine dihydrochloride and conjugated with transferrin, which were designed for the management of cerebral malaria, showed an enhanced uptake in the brain than the free drug in solution (Gupta et al., 2010). This can be explained by the fact that transferrin promotes the receptor mediated transport of the SLNs.
- The use of cationic bovine serum albumin (CBSA) as a ligand for the functionalization of SLNs have also proved to be a promising strategy for bypassing the BBB (Agarwal et al., 2011). Nonetheless, in this case, the mechanism for this enhancement in the penetration is not due to the use of receptor mediated mechanisms, but adsorptive transcytosis, as the positive charge of the albumin can interact with the negative charge of the surface of the endothelial cells.

2.2.4.3. Lipid nanocapsules. Finally, lipid nanocapsules can be found as the last type of lipid-based nanocarriers. They have the advantages of being more stable than liposomes and being able to encapsulate greater amounts of lipophilic drug. It is because they have a lipoprotein-like structure, with an oily core surrounded by a rigid membrane of polymer or tensioactive (Huynh et al., 2009).

In 2020, Elhesaisy and Swidan proved that they were able to reduce the immobility time of mice when they forced them to swim in a beaker, a stressful situation in which animals tend to desperate, resign and stop moving, after the administration of lipid core nanoparticles loaded with trazodone hydrochloride. In fact, the immobility time for the group without treatment was 158 ± 15 s, for the group which received a solution of free trazodone was 128 ± 12 s, but in the group treated with the nanocapsules the immobility time dropped until 88 ± 8 s (1.8-fold lower than the control group). So, researchers conclude that these carriers were a promising alternative for controlling depression (Elhesaisy and Swidan, 2020).

From May 2018 to April 2020, the project BIONICS worked in the development of lipid nanoparticles with anti-oxidant effects for the treatment and prevention of post-stroke side effects (EU Publications Office, 2020). The reason for this is that the current treatment for ischeamic stroke, the administration of tissue plasminogen activator or the physical removal of the thrombo, can restore the blood flow in the affected area, but it cannot avoid the damage of brain tissue due to the release of reactive oxygen and reactive nitrogen species. Preliminary results show that the new carrier was able to target both BBB and neuronal cells and, now, the group is working to prove its antioxidant and neuroprotective effect (EU Publications Office, 2020).

2.2.4.4. Polymeric nanoparticles. Polymeric nanoparticles can be divided in two groups depending on their structure: nanospheres (a solid polymeric matrix) or nanocapsules (an inner core surrounded by polymer). Several biodegradable and biocompatible polymers have been studied for the development of CNS nanocarriers, i.e. polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), chitosan and polycaprolactone (PCL), among others (Alexander et al., 2019; Sánchez-Dengra et al., 2020). The next bullet points show examples of polymeric nanocarriers developed with the polymers mentioned above:

- Polylactic acid (PLA): PEGylated PLA nanoparticles modified with an anti-transferrin receptor antibody and loaded with amphotericin B were developed in 2015 for the treatment of fungal meningitis. The PEG modification increases the stability of the particles in the blood and the anti-transferrin receptor antibody promotes the receptor-mediated transport through the BBB. The studies carried out with this formulation showed that the particles were able to significantly reduce the necrosis of brain tissue after 15 days of infection and increase the survival rate of mice whose lethality rate dropped from 100% in day 16 post-infection in the untreated group to 50% after 24 days (Tang et al., 2015).
- Polylactic-co-glycolic acid (PLGA): In the prospect of treating Alzheimer's disease, PLGA nanoparticles loaded with curcumin were prepared by Barbara and co-workers in 2017. Curcumin has proved to be able to inhibit the formation of Aβ plaques and disaggregate those already formed, but, as many other drugs, it has a low ability to cross the BBB. The new particles, which were modified with a peptide ligand (g7) for BBB crossing, showed to be able to reduce the number of Aβ aggregates in an in vitro model with hippocampal cells. Besides that, they seemed to reduce the inflammatory process associated to Alzheimer's disease. Nonetheless, further studies in in vivo models are needed to obtain further conclusions (Barbara et al., 2017).
- Chitosan: Chitosan is a natural polysaccharide, which can be obtained after the deacetylation of chitin extracted from crustacean shells and has been studied for the treatment of many conditions, mainly Alzheimer's disease and Parkinson's disease (Ojeda-Hernández et al., 2020). Nanoparticles of chitosan loaded with rotigotine have proved that, after being administered intranasally, are able to reduce catalepsy, akinesia and improve the swimming ability in a Parkinson-induced animal model. Furthermore, pharmacokinetics studies showed a greater accumulation of rotigotine in the brain in comparison with the intranasal administration of the free drug or the administration of the particles by other ways (Bhattamisra et al., 2020).
- Polycaprolactone (PCL): In vitro studies carried out in three different cell lines with PCL nanoparticles loaded with clozapine, an antipsychotic drug used in the treatment of schizophrenia, show that this type of formulation may be a valuable alternative for the management of this pathology. The PEGylated particles were not toxic nor immunogenic and increased the permeability of clozapine in hCMEC/D3 monolayers (Łukasiewicz et al., 2019). No in vivo studies were carried out with these particles which hinders the possibility of using them in humans.

2.2.4.5. Inorganic nanoparticles. Inorganic nanoparticles prepared with metals, metal oxides or silica are useful for, both, diagnosis and treatment of pathologies affecting the CNS, this is, they can act as theragnostic devices. Nonetheless, they have the big drawback that, in contrast to those nanoparticles mentioned previously, they are not biodegradable and they can be toxic (Alexander et al., 2019).

Due to their surface plasmon property, gold nanoparticles can absorb and emit light at different wavelengths according to their size, shape and aggregate status (Sánchez-Dengra et al., 2020). Besides that, the surface plasmon property also makes this kind of particle ideal for photothermal therapy as the light they absorb can be converted into heat (Pissuwan, 2017). The photothermal therapy with gold nanoparticles has been tested in several in vitro and in vivo models of glioblastoma, but, for translating the findings obtained in those models to the treatment of human beings several challenges must be faced, such as: the several barriers that the irradiating light needs to cross until it reaches the particles in the tumor without damaging any other cerebral structures (Bastiancich et al., 2021).

Magnetic nanoparticles prepared from iron oxides have also been studied as a thermal therapy for the treatment of glioblastoma or as

contrast agents for imaging techniques (Lombardo et al., 2020). In addition, these nanoparticles can be used as a driving force for promoting the passage of other types of nanocarriers through the BBB (Sánchez-Dengra et al., 2020). For instance, magneto-liposomes entrap a magnetic core in its inner part, which facilitates the delivery of drugs across the BBB, as proved by Saiyed et al. and Ding et al. in 2010 and 2014, respectively (Ding et al., 2014; Saiyed et al., 2010; Thomsen et al., 2015). More recently, in 2023, these magneto-liposomes have been studied for the treatment of brain cancer (Liu et al., 2023; Park et al., 2023). In one of the studies, it was observed how the use of a magnetic field was able to increase the accumulation of the liposomes in the brain in comparison to the non-magnetic ones (Park et al., 2023).

Mesoporous silica nanoparticles (MSNs) have a high surface area, can load big amounts of cargo, are biocompatible and are easy to functionalize. Because of that, a lot of researchers try to use this system for the development of new nanocarriers (Alexander et al., 2019). In 2016, an in vitro study carried out in two different monolayers, which are able to simulate the BBB (MDCK and RBE4 cells), showed that bare MSNs had low permeability and external functionalization was necessary to improve BBB penetration (Mendiratta et al., 2019). After that, several studies with functionalized MSNs have been carried out. For instance, lactoferrin-MSNs proved to reach the brain due to the use of the receptor-mediated pathway in a triculture in vitro model (Song et al., 2017). Also, Ri7 antibody-MSNs increased the drug delivery to the brain by means of binding to the transferrin receptor (Mendiratta et al., 2019).

2.2.4.6. Dendrimers. Dendrimers are three-dimensional and regular polymeric macromolecules with three different areas: (A) a central core, (B) branches and (C) surface groups. The number of ramifications in a dendrimer defines its generation and the spaces that there are in between the branches can be used to transport other molecules (Bors and Erdő, 2019; Sánchez-Dengra et al., 2020).

The most studied dendrimer is poly-amidoamine (PAMAM) (Bors and Erdő, 2019). In 2016, Xu and collaborators loaded PAMAM with doxorubicin and did several in vitro and in vivo studies to prove its efficacy against glioblastoma. As surface groups, they selected two molecules: borneol, whose mission is to open the tight junctions in between the endothelial cells of the BBB, and, folic acid, to target the dendrimers to cancer cells, as they overexpressed the folic acid receptor. The in vitro studies showed that the nanocarriers prepared by Xu and collaborators were not toxic for BBB cells, but they were able to kill the glioblastoma cells. Besides that, a sustained released of doxorubicin was observed when the dendrimers were placed in pH 5.5 buffer and the permeability of the drug in HBMEC monolayers was enhanced. Once in the in vivo studies, dendrimers showed a greater accumulation in brain and tumor than the free drug, a significant reduction of tumor volume and an increase in the survival of the animals tested (Xu et al., 2016).

2.2.4.7. Cyclodextrins. Cyclodextrins are cyclic polysaccharides used for delivering lipophilic drugs in an aqueous environment, as they are highly hydrophilic in their surface, but more hydrophobic in their inner part. Furthermore, cyclodextrins are able to interact with lipid membranes, so, they can be used to increase BBB permeability by means of altering its membrane fluidity (Bors and Erdő, 2019; Vecsernyés et al., 2014).

Recently, a new complex of crocetin and γ-cyclodextrin was proposed for the treatment of Alzheimer's disease. The in vitro evaluation of the new complex showed that it was nontoxic and it was able to reduce the levels of Aβ in 7PA2 cell line. The pharmacokinetic evaluation in rats showed that, after an intraperitoneal injection, the maximum concentration in plasma of crocetin was 43.5 times higher when it was administered in the cyclodextrin complex than when it was administered on its own and the AUC was also 13.1 times higher. In terms of biodistribution, it was seen that the crocetin-γ-cyclodextrin complex was able to penetrate the BBB and reach the brain after its administration (Wong et al., 2020).

2.2.4.8. Quantum dots. Quantum dots (QDs) are small nanosystems ranging from 2 to 10 nm with semiconductor properties. In a similar way that gold nanoparticles, QDs can emit light in different wavelengths depending on their size, shape, and composition, because of that they have been proposed as theragnostic tools (Badıllı et al., 2020).

In the treatment of CNS pathologies, QDs have been explored to target and identify brain tumors, to detected areas affected by ischemia after a stroke or to treat HIV-associated encephalopathy (Alexander et al., 2019; Xu et al., 2013). In the last case, quantum dots conjugated with transferrin, as a targeting ligand to BBB, and saquinavir, as an antiretroviral drug, have proved to efficiently cross the BBB and inhibit HIV replication in infected PBMC cells, using a triculture in vitro model (Xu et al., 2013).

2.2.4.9. Nanogels. Nanogels can be defined as nanoparticles composed of a cross-linked hydrophilic polymer network (Ribovski et al., 2021). Its capacity to retain water promotes nanogels biocompatibility and facilitates drug release. Nonetheless, this type of nanocarrier have been less studied for the treatment of pathologies affecting the CNS (Alexander et al., 2019). In June 2021, Ribovski et al. published an article in which they discuss the influence of nanogel' stiffness in BBB permeability. Briefly, they prepared 4 types of nanogels with different percentages of polymer and different polymerization times. Once obtained, they analysed the permeability of the different particles in a hCMEC/D3 BBB in vitro model. They saw that the low stiffness promotes intracellular trafficking and exocytosis through the cell monolayers (Ribovski et al., 2021). So, soft nanogels would be the most promising ones for developing drugs directed towards the CNS.

2.2.4.10. Nanoemulsions. Nanoemulsions (NEs) are composed of kinetically stable dispersions of two immiscible liquids (Karami et al., 2019). They can transport both hydrophilic and hydrophobic drugs and the smaller are the droplets of the emulsion, the greater is its stability. The mechanisms by which this type of nanocarrier can promote BBB permeability are:

- Lipid exchange, because of the interactions between the lipid phase of the NEs and the lipids of the endothelial cell's membranes (Karami et al., 2019).
- Carrier-mediated or receptor-mediated transport, which can occur if the external phase of the NE is decorated with a specific ligand (Karami et al., 2019).
- Adsorptive-mediated transcytosis, if the hydrophilic head of the lipids forming the droplets of the NE are positively charged (Karami et al., 2019).
- Efflux transport inhibition, as the droplets of the NEs can mask the drug from its efflux transporter and some surfactants present in the NE, i.e. polysobate 80, are well-known Pgp inhibitors (Karami et al., 2019).

NEs have been studied for the treatment of: brain tumors, neurodegenerative disorders, HIV-associated CNS disorders, ischemic stroke and schizophrenia (Karami et al., 2019). Several examples of NEs intended for the treatment of those pathologies is shown in Table 2.

2.2.4.11. Viral vectors. Finally, in terms of gene therapy, viral vectors have become extremely popular for the treatment of neurological disorders due to its high transfection efficiency and its long-term expression (Ahlawat et al., 2020). The adeno-associated virus serotype 9 (AAV9) is the most promising vector for CNS gene therapy as it has proved to be able to cross the endothelial cells by active transport without disrupting the BBB (Bors and Erdő, 2019; Fu and McCarty, 2016).

AVV9 has been tested for the treatment of spinal muscular atrophy

Table 2
Examples of nanoemulsions intended for the treatment of CNS diseases (Karami et al., 2019).

Disease	Nanocarrier	Outcomes
Brain tumors	Kaempferol mucodhesive NE	Increased brain levels after intranasal administration. Reduced glioma (C6 cell line) viability.
	Chloroaluminun phtalocyanine NE	Reduced glioma (U87 cell line) viability.
	Paclitaxel ClinOleic®	Reduced glioma (U87 cell line) viability. Selectivity towards cancerous cells.
	Honokiol NE	Inhibition of tumor growth in vivo.
Neurodegenerative disorders	Oridonin NE	Less Aβ plaques and Aβ deposition. Restored construction behaviour.
	Rivastigmine NE	Increased brain levels after intranasal administration.
	Thymoquinone-rich fraction NE	Less Aβ generation and more Aβ degradation. Increased antioxidant levels.
	Selegiline NE	Increased antioxidant enzymes. Higher dopamine levels in Parkinson's disease rats.
	Riluzole NE	Increased brain levels after intranasal administration.
HIV-associated CNS disorders	Saquinavir mesylate NE	Increased brain levels after intranasal administration.
	Indinavir NE	Increased brain levels after intravenous administration.
	Atovaquone NE	Increased bioavailability after oral administration. Reduced parasitemia and less brain cysts in a toxoplasmosis.
Ischemic stroke	Thymoquinone mucoadhesive NE	Increased brain levels after intranasal administration. Better motor skills.
	Olmesartan NE	Increased brain levels after oral administration.
	Quercetin mucoadhesive NE	Better motor skills. Lower infarction volume and less hematoma. Increased antioxidant capacity.
Schizophrenia	Quetiapine NE	Increased brain levels after intranasal administration.
	Risperidone NE	Increased bioavailability and brain levels after intraperitoneal administration. Early onset of antipsychotic action. Less locomotor side symptoms.

(SMA) in several clinical trials (Chen et al., 2021). SMA is a genetic disease affecting the alpha motor neurons of the spinal cord and brainstem. The degeneration of these neurons causes several difficulties in speaking, walking, breathing, and swallowing; it can lead to paralysis and death too, being the leading cause of mortality in infants (Pattali et al., 2019). Early-diagnosed patients treated with AAV9 showed a better motor behaviour and an increase in its rate of survival. Nonetheless, more efforts are needed before obtaining the final vector for treating this disease, as there were patients who developed antibodies against the vector and this may cause severe side effects (Pattali et al., 2019).

3. Discussion

As said in the review, in the last two decades, there has been a considerable increase in the prevalence of most diseases that affect CNS which highlights the need for new treatments to combat them. Nonetheless, about 85% of CNS trials fail, which is the second highest failure rate just after the oncology trials (WCG Institute, n.d.). Among the reasons for these failures, we can find: problems with the target, lack of biomarkers, problems with the design of the study, issues with the transition from animals to human because animal models tend not to be as complex as human beings and drugs not crossing the BBB (Cummings, 2018; Savitz and Fisher, 2007; Wegener and Rujescu, 2013). In our opinion, the development of strategies to allow or increase the access of substances to the CNS would solve most of the failures. Nonetheless, trying to overcome these failures, industries tend to opt for a repositioning strategy, a more cost-effective and time-saving alternative also known as drug repurposing or drug reprofiling (Morofuji and Nakagawa, 2020).

Although having been used as interchangeable terms, there is a subtle difference between repurposing and repositioning. In repurposing, a drug already approved and without suffering any molecular modification is reapproved for a different indication, while in repositioning, the drug suffers some change in its structure before being approved for another indication (Morofuji and Nakagawa, 2020). Historically, reposition has happened unintentionally, but, recently, researchers and industries have realized its benefits and used it with those drugs which have proved to be safe, but not effective, in their clinical trials. This is the reason why, year after year, the number of articles including on their keywords "drug repositioning" increases (Morofuji and Nakagawa, 2020). In the field of CNS treatments, approximately 30% of the drugs have been repurposed two or more times (Morofuji and Nakagawa, 2020), mainly because once the drug crosses the BBB it is easier to find a new target for it. Thus, this trend, although having clear advantages in the treatment of pathologies of the CNS, would reduce the investment of big industries for the development of new devices to increase the access of substances to the CNS.

When talking about nanocarriers, the most sophisticated and non-invasive strategy to improve the treatment of pathologies affecting the CNS, the articles published in this field have increased by more than 80% in the last 10 years (results after searching: "nanocarrier" and "brain" in Pubmed). This tendency makes us think that, there is a clear interest in knowing about these formulations. So, probably in the next five or ten years the knowledge about them will continue increasing. However, if the knowledge is obtained from public institutions, such as universities or research centres, the key for a global benefit will lay in the results transfer from the public to the private ambit. It is useless to accumulate tons of knowledge, if society cannot benefit from it. From some institutions, great work is being done and, increasingly, university researchers patent their ideas before publishing them. This fact can greatly help industries to notice them, buy them and work on the development of new nanocarriers with certain guarantees of success.

A quite interesting idea would be to create a database in which the results of different nanocarriers with the same drug can be grouped and easily compared. Table 3 clusters the results of different formulations loaded with docetaxel. The improvement in the exposition of the brain to the drug (AUC) can be effortlessly checked and, in this case, the best nanocarrier would be the (PRINT)®-PLGA nanoparticles. Nonetheless, for other drugs, the best formulation may be another. In addition, this comparison has some limitations:

- The carriers have different kinds of functionalization, so they are not really comparable.
- Depending on the study checked, different protocols for measuring the biodistribution of the drug are found. So, the AUC are measured at different times.
- Some researchers, who develop nanocarriers, do not measure the biodistribution of the particles or they show the increase in concentration at a particular time, but not in AUC. When checking the docetaxel nanocarriers, we have found a couple of articles, with a dendrimer (Gajbhiye and Jain, 2011) and a nanoemulsion (Gaoe et al., 2012), in which they presented the results like that.

Table 3
Comparision of the AUC improvement for different nanocarriers loaded with docetaxel.

Nanocarrier	Composition	Functionalization	AUC increase (ratio)	REF
Liposomes	o Soybean phospholipids Cholesterol	Ascorbic acid	3.24-fold	(Xiao et al., 2019)
Solid lipid nanoparticles	o Glyceryl monostearate Vitamin E Soy lecithin	Folic acid	5.17-fold	(Venishetty et al., 2013)
Polymeric nanoparticles	o PLGA	Aspartic acid Piperine	6.52-fold	(Singh et al., 2019)
	o Maltodextrin Poly(methacrylic acid) (PMAA) Polysorbate 80 (PS 80) Dodecylamine Ethyl arachidate		5.04-fold	(He et al., 2017)
	o (PRINT)®-PLGA		13.13-fold	(Sambade et al., 2016)
Inorganic nanoparticles	o Gold nanoparticles Liposomes (Egg lecithin and cholesterol)	Transferrin	3.40-fold	(Sonkar et al., 2021)
Quantum dots	o Quantum dots Liposomes (DPPC and cholesterol)	Arginine–glycine–aspartic acid (RGD) peptide	8.03-fold	(Sonali et al., 2016)

Of course, the information obtained from the propose database should be combine with the information from tests in disease models to evaluate, not just the drug penetration to the CNS, but also its efficacy. Moreover, the data clustered in this database should be divided in two groups depending on the availability of in vitro or in vivo information about the behavior of the carriers. In many cases, when the formulations are promising in vitro and they are tested in vivo they are not as good as the seemed. It is because an ideal in vitro model should have all these characteristics (Sánchez-Dengra et al., 2021):

1. Tight connections, which result in high selectivity and electrical resistance.
2. The presence of the same inflow and efflux transporters found in an alive BBB, as well as a polarized structure.
3. The capacity to distinguish between substances based on their permeability.
4. Ability to react to aggression and control its morphology in reaction to blood flow shear stress.
5. Reproducibility, predictability, accessibility, and cost-effectiveness.

Nowadays, the ideal model does not exist, but great efforts are being done to obtain an in vitro model with most of the characteristics (Jiang et al., 2019; Passeleu-Le Bourdonnec et al., 2013; Sharma et al., 2019).

In our opinion, the ideal approach to increase the access of substances to the CNS should combine the use of nanocarriers with other strategies to increase drug penetration such as, the physical opening of the BBB with ultrasounds and microbubbles or the nasal administration to get a non-invasive direct administration to the CNS.

4. Conclusion

Along this document, an extended revision of different strategies to allow or increase the access of substances to the CNS has been done. It can be seen that there are several options which can be used and are able to increase the levels of drug in the brain. So, when trying to treat a pathology of the CNS, both the development of new molecules and its combination with a proper method to overcome the BBB must be done.

The current therapeutic treatment of diseases of the central nervous system such as glioblastoma, Parkinson's, Alzheimer's, schizophrenia has a lot of possibilities for improvement. The great amount of research in this field will allow some of those strategies to reach the clinic and many of these diseases can benefit in the future from the advantages offered by these new formulations and forms of administration in order to achieve the definitive cure or the improvement of the quality of life of patients.

CRediT authorship contribution statement

Bárbara Sánchez-Dengra: Investigation, Visualization, Writing – original draft, Writing – review & editing. **Isabel González-Álvarez:** Funding acquisition, Project administration, Conceptualization, Validation, Writing – review & editing. **Marival Bermejo:** Funding acquisition, Project administration, Supervision, Writing – review & editing. **Marta González-Álvarez:** Project administration, Supervision, Conceptualization, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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