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The "fate" of polymeric and lipid nanoparticles for brain delivery and targeting: Strategies and mechanism of blood–brain barrier crossing and trafficking into the central nervous system

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ABSTRACT

Drug delivery to the brain represents one of the most important challenges in the field of nanomedicine, as the study and planning of nanocarriers able to cross the blood brain barrier are topics at the cutting edge of technology and innovation. In this review, we analyze the interventions and progresses in the field, by analyzing the choice of the polymer, of the ligands and the main relevant *in vivo* and *in vitro* experiments. A critical overview of these aspects will help in better understanding the status of nanomedicine in the application to central nervous system pathologies along with the future directions.

1. Introduction on central nervous system drug delivery and blood brain barrier

The research of efficacious non-invasive therapy for the treatment of neurodegenerative diseases is one of the most important topics faced in the last years by the pharmaceutical technology. The interest in this topic was triggered by the prevision that the number of people affected by disorders of the central nervous system (CNS) at the end of the 20th century [1] should significantly increase owing to increasing of the life expectancy. The prediction that approximately 50% of the population should develop Alzheimer's disease [2] at some point of their life in the future, emphasizes the seriousness of the future situation.

The blood–brain barrier (BBB) is a barrier designed to protect the CNS from microbial contamination and toxic agents. Unfortunately, the BBB hampers a lot of effective drugs to reach the CNS. The BBB consists of walls formed by capillaries that isolate the brain compartment from the bloodstream. The low permeability properties are due to an anatomical structure characterized by tight junctions, presence of efflux transporters and low level of enzyme activity. Capillaries within the CNS lack of intercellular clefts and fenestra and show low pinocytotic and macropynocitotic activity, just the opposite of the rest of the body capillaries [3].

In the past, the BBB was considered as a very static membrane, impermeable to hydrophilic substances and permeable only to lipophilic molecules. Nowadays, BBB structure is considered as a very dynamic interface capable to allow nutrients and substances to enter the CNS by means of different influx pathways (paracellular aqueous pathway transporting water-soluble agents; transcellular lipophilic pathway transporting lipid-soluble agents; transport protein pathways for glucose, aminoacids and purines) or more complex mechanisms such as specific-receptor mediated trans- or endocytosis (insulin or transferrin) or adsorptive trans- or endocytosis (albumin and other plasma proteins).

Toxic molecules or pathogens can be "pushed out" by efflux systems, such as P-glycoprotein (P-gp), multidrug resistance proteins (MRP) or organic anion transporter (OAT) efflux pumps.

Unfortunately, the efflux systems often represent a limit for the

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effectiveness of the treatment of brain diseases because many drugs (proteins and gene materials) cannot cross the BBB owing to the presence of P-gp and other efflux systems or for the lack of specific active transport influx systems.

2. Nanotechnology for blood brain barrier crossing and central nervous system targeting

Even if, as reported by Pardridge [1], less than 1% of both industrial and academical research projects on neuroscience displays of a BBB crossing and targeting aim, the study and progress of drug delivery strategies to cross the BBB are supposed to be widely addressed. Non-invasive techniques based on colloidal carriers could represent a huge potential, since nanocarriers (polymeric nanoparticles, nanoliposomes, solid-lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), micelles, nanogels and dendrimers) could protect the drugs (or gene material) and deliver them to CNS [4–19].

Passive targeting of CNS is based on nanocarriers, not engineered on surface, allowing passive diffusion, through the enhancement of a drug's plasma concentration, leading to a larger gradient at the BBB and consequent increase in drug amount entering the CNS [20].

Active targeting of the CNS is on the contrary found on surface engineering with suitable ligands (Fig. 1) [21,22]. Nanocarriers with proper ligands are able to cross the BBB without apparent damage [4], to ensure targeting to a specific tissue [23–26] and can be used to deliver drugs or genetic material into the brain [27].

The pathways for active nanocarriers transport across the BBB were hypothesized to involve receptor-mediated endocytosis [28], fluid phase endocytosis or phagocytosis, carrier mediated transport or by absorptive-mediated transcytosis.

The most common strategy for nanocarrier targeting to the brain is receptor-mediated endo-/transcytosis. This pathway consists of i) interaction of the surface ligands onto nanocarriers (transferrin, transferrin-receptor binding antibody, lactoferrin, melanotransferrin, folic acid and a-mannose) with specific receptors; ii) formation of endocytotic-vesicles enveloping nanocarriers; iii) transcytosis across the BBB; iv) exocytosis of nanocarriers in CNS parenchyma [2,29–35]. Even if this approach represents the most promising in terms of "BBB crossing pathway", it does show some limitations. In fact, all receptor-based approaches are based on extremely high and strong linkage between the receptor and the ligand attached onto the NPs surface. If this binding is too high and therefore very tight bonds are produced, low exocytosis rate are supposed. *In vivo* models [36] highlighted a higher percentage of NPs inside capillary endothelial cells compared to NPs inside the CNS parenchyma. Moreover, a possible saturation mechanism due to the presence of the endogenous ligands to the receptor could occur, thus hampering the efficiency of receptor-mediated endocytosis. This concept is especially related to the use of mAb conjugated to nanocarriers to target receptors, present at the BBB level and triggering interaction between targeted systems and BBB-membrane. In the past, the major objective for receptor-mediated transcytosis was to discover and take advantage of the most specific and efficacious mAb to select receptors at BBB level. On the contrary, today, it is almost clear that the importance of such specificity and the strength of mAb/receptor bond lose their pivotal role. A certain affinity to receptors is still important to trigger/start endo/transcytotic pathways, but it is much more "functional" to let mAb modified nanocarriers able to free from receptor-binding and to perform exocytosis after BBB crossing.

Remarkably, the use of certain kinds of mAb (i.e. OX26) has been recently considered [36] with criticism, since OX26 was confirmed [37] to accumulate at the brain capillary endothelial cells and not in the parenchymal compartments. After in situ administration in mice, the total amount of a drug-conjugated to OX26 was associated with brain capillary endothelial cells [38], therefore dissociation from their specific receptor could be difficult due to the high affinity with the antibody.

3. *In vitro* proof-of-concept

As first pre-screening, *in vitro* test are performed aiming to study interaction, behavior, uptake and toxicity of nanocarriers.

Important efforts of many researchers were developed in order to exploit the potentiality of lipid and polymeric nanoparticulate systems in overcoming the BBB for the delivery of different drugs such as anti-inflammatory and anticancer compounds. The design and the optimization of lipid nanoparticles was deeply investigated exploiting the potentiality of the factorial design [10,15,16,39]. In order to optimize the carrier for the delivery of drugs or gene materials, different strategies were developed such as the addition

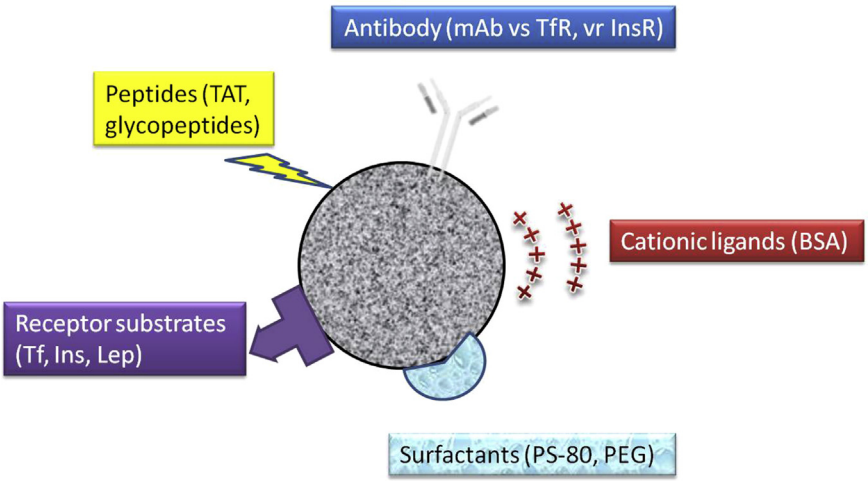

Fig. 1. Nanocarriers for brain targeting: schematic representation of the strategies for blood brain barrier crossing; Tf is transferrin, Lep is Leptin, TfR is Transferrin receptor, Ins is insulin, InsR is insulin receptor, BSA is Bovine Serum Albumin, PS-80 is polysorbate 80, PEG is poly-ethylenglycol.