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The physics of drug-delivery across the blood-brain barrier

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publication in Therapeutic Delivery. There is plenty of flexibility regarding the title of the piece.

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"The physics of drug delivery across the blood brain barrier"

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Key words: Blood Brain Barrier, nanocarriers, ultrasound, magnetic field, microbubbles

The challenging goal of trespassing the Blood Brain Barrier (BBB) is being faced using physical triggers to enhance drugs penetration either as such or loaded within Nanocarriers (NCs). NCs as nanotechnology-based drug delivery strategy, have attracted increasing attention in biomedicine because their dimension approaches the size scale of the biological components to which targeted delivery is desired. In particular, drug nanodelivery systems can be considered the new frontier for the controlled release of various therapeutic substances for the treatment of central nervous system (CNS) diseases [1].
In spite of 25 years of intensive research in the field of nanomedicine, with the exception of few nanotherapies, most applications have failed to translate into clinics. Indeed, in particular, few NCs are able to cross the BBB and to penetrate into the CNS tissues [2].
To get a clinical effect, in fact, an almost unlimited series of 'traps' have to be escaped by the NCs before BBB permeation: after intravenous injection degradation in the bloodstream, 'coronal' protein adhesion, overall distribution, sequestration in liver, spleen, kidneys, intracellular localization and many other undesired effects occur, each one critically restricting the overall success of the therapy [2].
Alternatively to systemic administration, 'topical' approaches driven by physical triggers have been investigated, based on the trespassing of the biological barriers, which covers and protect the target cells.

To promote the drug and/or biological molecules penetration across the BBB two different (but possibly complementary) strategies can be followed:

1) the 'NanoSize' strategy, using carriers whose dimensions are so limited that transmembranal passage occurs both via passive (by direct plasma membrane) or active (endocytosis, pinocytosis, etc) penetration;
2) the 'NanoHole' strategy, producing a local and temporary barrier disruption by osmotic, pharmacological or physical means.

The NanoSize strategy is based on the idea that nanocarriers may act as Trojan horses: after reaching their site of action by passive processes, they may at best differentially accumulate in the location of interest and facilitate the drug intake throughout the body by physiological systems.
The NanoHole strategy mainly promotes a variety of mechanisms allowing safe temporary opening of the membrane junctions and membrane structure. As a matter of fact drug penetration through the BBB could be significantly improved providing a proper physical vector, including thermal, ultrasonic (either focused or not) and electromagnetic fields is applied. In this context, skin penetration has been extensively studied in the past and some suggestions may be exploited for promoting BBB trespassing, such as physical based 'phoresis: both Ultrasound (sono-phoresis) or electrical field (electro- or iono-phoresis) are used to get an efficient transcutaneous drug transport [3].

The BBB scenario
The Blood Brain Barrier is formed by the endothelial cells confining the cerebral capillaries and by the nearby astrocytic end-feet processes, perivascular neurones and pericytes [4]. The two sides of the membrane are the luminal (blood side), with a reduced rate of pinocytosis preventing entrance [5] and the abluminal or basal one (brain side), which allows a very limited transport of substances in both directions. Capillaries are linked together by tight junctions whose electrical resistance is as high as 2000 ohm/cm^2 [5].
BBB allows the passive diffusion of water, most of gases, and lipid soluble molecules, as well as the selective transport of some molecules such as glucose and aminoacids that are crucial for neuronal function. However BBB prevents the uptake of most therapeutic molecules by active transport mechanisms and it actually excludes ~100% of large-molecule neurotherapeutics and more than 98% of all small-molecule drugs, such as anticancer drugs, antibiotics, anti Alzheimer's drugs and anti Parkinson's drugs from the brain. Particularly, neurotherapeutic molecules such as rivastigmine or tacrine, that might be effective in neurological diseases, do not cross the BBB in adequate amounts.
Much research is therefore focused on the delivery of drugs across the BBB either invasively or non invasively.
Concerning invasive methods, direct injection of drugs to BBB through intra-thecal or intracerebroventricular fluids is feasible only in surgical settings with possible severe side effects, such as infection and trauma. In the absence of any effective targeting, however, most of the systemic applications fail in delivering a clinically significant drug dose.
Non-invasive methods often rely on chemical modification of drugs, e.g. prodrug synthesis, or on the inhibition of efflux transports. As an example, intranasal delivery, early used by W. Ewart in 1998 [6], needs penetration enhancers and a significant fraction of drug is removed by ciliary clearance and not fully absorbed.
Being the concentration gradient the only driving force, a clinically significant dose of 'naked' drug is hardly deliverable using shortcuts like nasal delivery because the administration site is far from the disease site (cerebral cortex for Alzheimer's, substantia nigra for Parkinson's disease).

Intranasal delivery of nanocarriers by inhalation and transmission through olfactory and trigeminal nerve pathways may improve the drug delivering effectiveness, as has been recently investigated [7].
External physical triggers able to increase the trespassing of BBB by opening temporary pores [8] may overcome the present limitations to nanocarriers penetration and might be used to improve drug delivery across BBB.

The NanoSize strategy

Nanoparticles have extensively been applied as nanocarriers to transport small molecules and even large peptides [9]. In the literature a number of different nanoparticles, e.g. polymeric [10], lipidic [11, 12], albumin- based [13] and metallic ones [14] are fully described. To allow nanoparticles to cross BBB a number of 'tricks' have been developed, based on surface modifications using surfactant coating (e.g. polysorbates or poloxamer) or protein covalent binding (e.g. apolipoproteins) [15].
Most of these NC applications require intravascular administration, and their short-range interplay with plasma and blood cells has to be accounted for in designing the NC structure [16]. Nanoparticles aggregation, possibly dangerously increasing their size, is one of the critical challenge. Accurate adjustments of the superficial charge are required, but any accidental variation in the external pH value can alter it dramatically. Adhesion of the blood proteins to the NC surface [2] may also cause size modification. This phenomenon can be avoided, or at least slowed, by grafting hydrophilic polymer to the nanoparticle surface, e.g. PEGylation, in which poly(ethylene glycol) (PEG) is grafted onto the nanoparticle surface producing 'stealth' nanoparticles showing an increased circulation time [16].

The NanoHole strategy

The ultrasound mediated barrier disruption for drug delivery can be exploited by different types of nanocarriers [17] among which the ultrasound-responsive microbubbles have been specifically designed to target CNS.
Focused Ultrasound (FUS), in conjunction with microbubbles, is the only technique that can induce regional localized BBB opening noninvasively. FUS consists in multiple intersecting beams of ultrasound directed and concentrated on a target. Whereas individual beams cross the tissue with no effect, the convergence of multiple beams of focused ultrasound at the focal point results in a huge local energy triggering important biological effects depending on the nature of the tissue and the ultrasound parameters.
FUS may thus have a huge impact in trans-BBB brain drug delivery. Chen & Konofagou [18] elucidated the interactions between ultrasound, microbubbles and the local microenvironment during BBB opening with FUS, by monitoring the mechanism of the BBB opening in vivo by MRI and passive cavitation detection (PCD). They showed that the BBB can be disrupted safely and transiently under specific acoustic pressures (under 0.45 MPa) and microbubble (diameter under 8 μm) conditions.
As a matter of fact, on November 9, 2015 a team led by T Mainprize and K Hynynen at Sunnybrook Health Sciences Centre in Toronto successfully used focused ultrasound to enable temporary and targeted opening of the blood-brain barrier (BBB), allowing effective delivery of doxorubicin-based chemotherapy into a patient's malignant brain tumor using Insightec's ExAblate Neuro system (see www.fusfoundation.org).
Recently also magnetic nanoparticles attracted increasing attention for their ability to precisely deliver drugs to specific sites of action by the application of an external magnetic field [19]

Although metallic NCs (e.g. superparamagnetic iron oxide, SPIONs) uptake increasing the intracellular iron content may have toxic effects expecially for oligodendrocytes [5], a possible alternative use can be devised. Recent literature suggest a close relationship between neurological diseases and heavy metal ion concentration [9]: the real challenge, under this point of view, would be that of manufacturing 'chelating' NPs which, once entered into the intracerebral liquid, could act as a 'metal scavenger' which can finally be expelled by the abluminal BBB side.

Final considerations

Although nanotechnological devices have raised serious concerns about their safety for human health [20] (Oberdörster defined the new science of 'nanotoxicology'), specifically due to their small size, the large surface area-to-mass ratio and the possible larger fraction of reactive electrons exposed at the surface, they are nowadays among the most promising therapeutic strategies.

Physics can be an important added value to enhance efficient drug delivery across biological membranes otherwise impenetrable, as showed by the success of the application of FUS to micro-bubble carriers.

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