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Mini-review

In silico models for nanotoxicity evaluation and prediction at the blood-brain barrier level: A mini-review

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ABSTRACT

Understanding and predicting the potential cytotoxic effect of various nanoparticles (NPs) at the blood-brain barrier (BBB) is an important challenge in modern nanotoxicology and nanomedicine. Different experimental and theoretical tools have been developed and implemented as cost-effective approaches for efficient nanotoxicity testing an area, where experimental and nanotoxicological data are still very sparse. NPs, as drug delivery vectors, can enhance or diminish drug permeation across the BBB due to their hydrophobic or hydrophilic nature. They are also prone to form lipophilic aggregates and agglomerates, which damage cellular membranes and components, and can accumulate inside of the living cells. As a result, various computational techniques, including molecular docking, molecular dynamics simulations, quantitative structure-activity/property relationship, have paved the way for investigating NP-cell interactions, predicting BBB permeation rates, and evaluating the potentially harmful effects of NPs on cells. This review discusses these *in silico* methods and computational strategies in an attempt to provide new insights and directions in the development of novel neuroactive molecular formulations (known as "nanodrugs" with "nanocarriers") for improving BBB permeation and minimizing cytotoxicity risks.

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Introduction

There is a growing interest in the emerging fields of nanobiotechnology and nanomedicine due to their multiple applications, which range from biology to neuroscience [1,2]. For the latter, the development of novel neurotherapeutic agents to combat diseases of the central nervous system (CNS) is vital. However, this is an extremely challenging task due to the blood–brain barrier (BBB), protecting the brain against the entry of various xenobiotic substances, that include bacterial toxins, endogenous harmful metabolites, drug-like molecules, and various nanoparticles (NPs) coming from the peripheral blood. This restriction in the transportation of substances through the BBB ensures the maintenance of brain homeostasis and normal cerebral function [3,4].

The functionality of the BBB is primarily determined by the brain's microvascular endothelial cells being strongly attached to each other by tight junction proteins, such as occludins, claudins, and zonula occludens (ZO) [5,6]. These cells play a pivotal role in

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the formation of the neurovascular unit together with neurons, pericytes, astrocytes, and extracellular matrix [7]. Additionally, tight junction proteins regulate the paracellular diffusion of hydrophilic substances, while small lipophilic drug-like molecules may permeate the entire BBB via a transcellular route [8].

Various pharmaceutical NPs have been used for controlled and targeted drug delivery to the brain across the BBB, ranging from functionalized carbon nanotubes to diverse formulated agents, and biocompatible polymers [9–12]. Since NPs are generally promising drug delivery vehicles and diagnostic tools, nanotoxicity has become a primary concern in the fields of rational drug design and biomedicine. Nanotoxic effects have frequently been reported in various *in vitro* experiments on mammalian cells and tissues due to the apoptotic events, such as generation of oxidative stress mediated by reactive oxygen species (ROS), inflammation, DNA damage, and intracellular deposition of non-biodegradable nanomaterial [13]. However, the biological activity of NPs is extremely difficult to assess on the basis of the corresponding bulk material's reactivity, as they tend to show a different behavior as a result of their heterogeneity in size and surface area [14]. These differences are potentially responsible for more diverse biological interactions, and may even lead to an already observed increase in nanotoxicity induced by NPs compared to the corresponding bulk material [14].

Therefore, the mechanism of action for different NPs including fullerenes, quantum dots (QDs) carbon nanotubes, metal-organic frameworks (MOFs), cyclodextrin (CD) formulations, etc at the BBB is a fundamental parameter to assess and predict their nanotoxic potential for the CNS. These cytotoxic issues have raised big concerns regarding the safe use of prospective NPs and nanomaterials, i.e. nanostructures with at least one dimension <100 nm, for many biomedical applications. In particular, a recent *in vivo* study involving a mouse model xenografted with human brain cancer cells clearly established the hyperthermal capabilities of exchange-coupled core-shell iron oxide NPs [15]. However, the changing biological activity of materials at the nanoscale might not be solely attributed to the heterogeneity in size and surface area – several other physical and chemical properties changing with size (e.g. surface characteristics, particle shape etc.) also affects different dimensions of the toxic behavior.

Moreover, the effects of NPs on inflammatory and immunological systems may include oxidative stress or pro-inflammatory cytotoxic activity in lungs, liver, heart, and brain [16]. Some lipophilic NPs could pass the BBB and could cause neurotoxicity [17,18]. On the other hand, various computational molecular models of NPs as drug delivery vehicles interacting with biomolecular targets provide pharmacologists and neurotoxicologists a valuable,

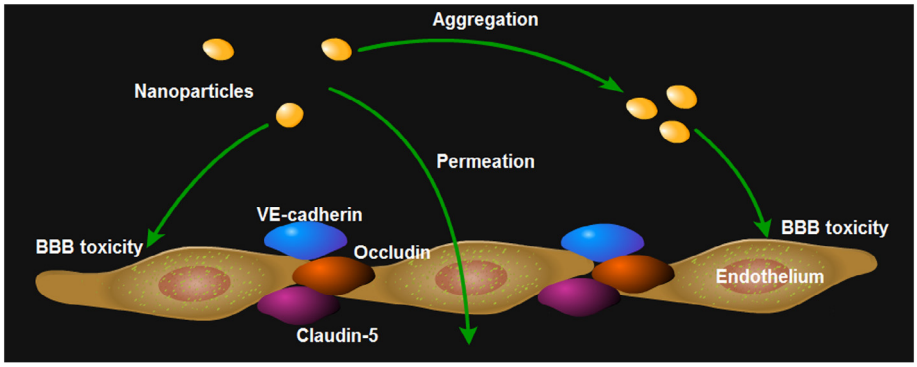

Fig. 1. Scheme of cytotoxic effects of NPs at the blood-brain barrier (BBB), which is represented by brain's microvascular endothelium with tight junction proteins (VE-cadherin, occludin, and claudin-5).

Table 1
Summary of *in silico* approaches to predict BBB permeation, aggregation of NPs, and their cytotoxicity.

Type of studied NPs	Type of endpoint investigated	Type of *in silico* approach employed	Main conclusion	Limitation of the study
Hydrophobic/hydrophilic	BBB permeation through cell membrane	Dissipative particle and discontinuous MD	Wrapped or embedded NPs	Coarse-grained model: approximate
Magnetic	BBB permeation through cell membrane	Steered MD (SMD)	BBB permeation of NPs driven by SMD force	All-atom model: small simulation interval
Liposomal	Drug distribution to the brain	Two-compartment PK	Increased drug concentration in the brain	Not very robust
Cyclodextrin-based	BBB permeation	Molecular lipophilicity potential	Improved BBB permeation of lipophilic NPs	Approximate
Carbon allotropes	BBB permeation	Molecular docking	Some NPs not interact with P-gp	Other BBB transporters not included
Peptides	NP aggregation	MD	Charge and H-bond driven aggregation	Coarse-grained model: approximate
Carbon allotropes	NP aggregation at the BBB	MD	vdW-dependent aggregation	All-atom model: small simulation interval
Metal oxides	NP aggregation	Nano-QSPR	Correlation of ζ-potential to NP agglomeration	Non-exhaustive experimental data
Carbon allotropes	Membrane damage	MD	Destructive lipid extraction and nanosheet cutting	All-atom model: small simulation interval
Anionic	Membrane disturbance	MD	Snorkeling effect due to lipid rearrangements	Coarse-grained model: approximate
Cyclodextrin-based	Membrane damage	MD and umbrella sampling	Cholesterol depletion by CDs	All-atom model: small simulation interval
Metal oxides	Membrane damage	QSAR	Correlation of membrane leakage with NP cytotoxicity	Outlier sensitive