A Review of Nanocarrier Brain-Targeting Ligands

Dania Abdel-Dayem[1,2]
[1]Department of Chemistry, American University in Cairo, Cairo, Egypt
[2]Department of Nanotechnology, American University in Cairo, Cairo, Egypt

Daniadayem@aucegypt.edu

Diverse brain diseases and disorders are becoming a significant global concern, typically remaining difficult to treat. In fact, neurodegenerative diseases such as Parkinson's disease are growing at an alarmingly high rate.[1] Moreover, the available treatments for both Parkinson's diseases and Alzheimer's remain greatly limited to symptomatic management rather than true cures. Similarly, neuroinflammatory conditions, such as multiple sclerosis, remain challenging to treat.[2] Furthermore, brain tumors are also difficult to manage owing to their intrinsic complex biological nature. The common challenge in all these diseases is the blood-brain barrier (BBB).[3 Despite the many promising therapeutic agents for brain diseases, their effectiveness is often limited by the BBB, an interface between the blood and brain. The BBB entails the brain blood capillaries which are surrounded by central nervous system endothelial cells, astrocytes, and pericytes that collectively form the BBB interface. Moreover, the brain endothelial cells are joined by tight junctions lacking fenestrations.[4] This barrier is highly selective hindering most large molecules, including antibody-based therapies, stem cells, gene therapies, and drugs larger than 500 kDa, from reaching the brain at the therapeutically required concentrations (only small, lipophilic molecules can cross easily).[4] Accordingly, there is an urgent need to create specialised drug delivery systems, such as targeted nanocarriers, to ensure the successful transport of pharmaceuticals. Otherwise, promising candidate drugs may fail due to poor delivery rather than inefficacy. Transport across the BBB occurs via different mechanisms, namely: paracellular transport; transcellular lipophilic transport; carrier-mediated transport (CMT); receptor-mediated transcytosis (RMT); adsorptive mediated transport (AMT). This work focuses on exploring the different ligands that may be used to facilitate the passage of nanocarriers across the BBB using CMT, RMT, and AMT mechanisms.[5] This work details the various ligands, their possible off-target effects, as well as their possible bioconjugation strategies. Furthermore, an overview of the emerging trends of using dual ligand strategies will be explored in addition to emerging BBB models that can be used for preclinical evaluations. These strategies aim to provide an overview and framework for the future design of nanocarriers for brain-targeted drug delivery.

References

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