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REVIEW

Intranasal drug delivery to overcome the blood–brain barrier

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The blood–brain barrier (BBB) displays strict, selective control of the passage of substances into the brain parenchyma due to the low permeability and large collection of transporters on the brain microvascular endothelial cells. Due to the restrictive nature of the BBB, pharmacotherapy of neurological disorders is greatly limited. As a result, a multitude of drug delivery systems (DDSs) has been developed, such as drug modification, BBB permeability modification, and bypassing the BBB. The intranasal drug delivery system (IDDS) appears to be the best approach to bypass the BBB and presents a non-invasive, relatively safe, and rapid method of delivering drugs to the brain. The IDDS is a promising approach for the delivery of therapeutic proteins and peptides to the brain. Further research is required to aid in the translation of preclinical results to the clinical setting.

Keywords: drug delivery systems, blood–brain barrier, drug modulation, intranasal drug delivery system, brain disorders

Introduction

The brain is a complex organ responsible for maintaining homeostasis in the body.[1] This is carried out by communication between neurons and different neuronal pathways.[2] Despite the central role played by the brain, it is particularly sensitive to changes in the cerebral micro-environment. Thus, the cerebral micro-environment must be maintained within a strict homeostatic range to prevent neuronal damage and preserve the physiological functioning of the brain.[1] This function is performed by the blood–brain barrier (BBB), a collection of tightly joined brain microvascular endothelial cells (BMECs) that express specialised transport systems and anatomical barriers.[2,3] The BBB displays strict, selective control of the passage of substances into the brain parenchyma due to the low permeability and large collection of transporters on the BMECs.[3] However, in some cases, the BBB is unable to maintain homeostasis in the cerebral micro-environment, leading to neurological disorders and diseases.

The role of the blood–brain barrier in neurological pathologies

Disorders and diseases of the brain are often severe and lead to significant disability.[4] In addition, these pathologies are challenging to treat as the pharmacotherapy of cerebral pathologies remains highly unsatisfactory.[5] This is due to the restrictive nature of the BBB preventing the entry of a multitude of substances. The BBB excludes approximately 98% and 100% of small molecule and large molecule drugs, respectively; greatly limiting the number of treatment options available.[6]

Many properties of the BBB contribute to its restrictive nature, namely the complexity, impermeability, lack of fenestrations, low rate of transcytosis, and efflux transporters.[7-9] Many components are necessary for a functional BBB, these include the BMECs, astrocytes, pericytes, and basement membranes, which results in a complex physical barrier to the delivery of drugs to the brain.[7] The BBB displays extremely low paracellular permeability and a lack of fenestrations due to the high expression of tight junction complexes joining adjacent BMECs to one another.[7,8] This greatly restricts the paracellular pathway.[7,8] Furthermore, the BBB displays extremely low levels of transcytosis, which further limits the entry of pharmaceuticals to the brain.[8] A substance that significantly penetrates the BBB may be a substrate for efflux transporter resulting in its rapid removal from the cerebral environment.[9] Thus, pharmaceuticals often do not reach therapeutic levels in the central nervous system.[4] As a result, a wide variety of drug delivery systems (DDSs) have been developed to improve drug delivery to the brain and subsequent management of brain diseases and disorders. Currently, several DDSs have been developed within three broad categories, namely drug modification, BBB permeability modulation, and bypassing the BBB.

Current drug delivery systems

Drug modulation

The first approach to improving drug delivery to the brain is to modulate the drug itself.[5] Earlier efforts in drug modification focused on increasing drug lipophilicity.[9] However, sequestration of the drugs in peripheral tissues limited delivery to the brain and the drugs often became substrates for the efflux transporter p-glycoprotein (p-gp).[5,9] Since then, more successful methods have been developed, such as drug conjugation. This involves conjugating a drug to a ligand or antibody that targets a specific receptor, often the transferrin or insulin receptors, allowing the drug to be delivered to the brain.[9,10] Colloidal systems or nanoparticle-based DDSs, such as nanoparticles and liposomes, have also been used in drug modification due to their small size and targeted delivery.[7] Nanoparticles are less than a micrometre in size and function as one unit.[7] Drugs must be adsorbed to the surface, enclosed in the shell or trapped in the core of the nanoparticle.[8] Functionalisation of the nanoparticles

involves the incorporation of surfactants or surface coatings to improve delivery to the desired organ by conferring certain properties to the nanoparticle, such as increased solubility, permeability, and half-life.[8] Liposomes are artificial vesicles, approximately 100–400 nanometres in diameter, that are composed of phospholipid bilayers.[8] Encapsulation of drugs into liposomal formulations has proven effective and many liposomal formulations are approved by the United States Food and Drug Administration and are currently on the market.[9] For example, Doxil, a liposomal formulation of doxorubicin, has been approved for the treatment of solid tumours.[9]

Blood–brain barrier permeability modulation

Another approach is to modulate the permeability of the BBB. The DDSs in this category are based on the principle of transiently increasing the permeability of the BBB to allow the entry of more substances into the brain.[11] These methods include chemical modulation using substances such as bradykinin and histamine,[12] tight junction modulation using specific peptides,[12] ultrasound-mediated BBB disruption,[13] and osmotic disruption of the BBB using a hyperosmotic mannitol solution.[12] However, a common limitation of these approaches is that the disruption is widespread, not focused to a specific brain region, allowing neurotoxic substances to enter the brain.[9,14] However, focused ultrasound disruption has overcome that limitation.[11]

Bypassing the blood–brain barrier

Another approach involves bypassing the BBB entirely, either using invasive methods such as intraventricular or interstitial delivery or a non-invasive method.[4,5] Invasive methods involve the direct injection of the drug into the brain, or implantation of a drug delivery device or a drug reservoir.[15] Implantation of a reservoir prevents the need for multiple invasive procedures as the drug can be delivered directly to the brain through the delivery device.[15] However, these methods carry risks associated with surgical procedures, neurotoxicity, haemorrhage, and the delivery device may become infected.[9,15] The intranasal route, however, does not carry these risks as it is non-invasive and does not require any special training to administer; in fact, the drugs can be self-administered.[15]

Intranasal drug delivery system

The intranasal drug delivery system (IDDS) takes advantage of the direct anatomical connection between the nasal cavity and the brain.[15] Intranasally administered drugs enter the brain by following the trajectory of either the trigeminal nerve or the olfactory nerve.[15,16] Trigeminal nerve fibres innervate the respiratory region of the nasal cavity and enter the cranial cavity through the cribriform plate.[16] The olfactory nerve fibres innervate the nasal epithelium as they project through the cribriform plate from the olfactory bulb.[16]

These nerve pathways converge in the cerebrospinal fluid surrounding the meninges and deliver drugs to the brain by bulk flow and arterial pulsations.[16] Drugs that follow the olfactory nerve pathway enter brain regions such as the hypothalamus, amygdala, and piriform cortex,[16] while drugs that follow the trigeminal nerve pathway enter the brain close to the pons and the olfactory bulb and may be delivered to posterior and anterior brain regions.[16] The intranasally administered drugs have been shown to have rapid and widespread distribution in the brain parenchyma, including those with large molecular weights.[16,17]

Advantages of intranasal drug delivery system

There are several advantages of IDDS, namely, the local delivery of drugs reduces peripheral side-effects and bypasses first-pass metabolism, which greatly improves drug bioavailability.[10,15] It is also useful in overcoming unfavourable pharmacokinetics such as low plasma stability, large volume of distribution, and short half-life.[18] Thus, it is a promising approach to delivering therapeutic peptides and regulatory proteins to the brain, such as insulin and glial-derived neurotrophic factor.[10,16] These have been shown to improve the presentation of Alzheimer's and Parkinson's disease, respectively.

Limitations of intranasal drug delivery system

Some limitations of IDDS have been reported, such as the difficulty of translating preclinical results to the clinical setting due to differences in the size of the nasal submucosal area relative to the nasal cavity between humans and preclinical animal models.[15] For example, the nasal submucosal area of rodents accounts for 50% of the nasal cavity, whereas it only accounts for about 3% of the nasal cavity in humans.[15] The difference is quite significant; however, intranasally administered radioactively labelled interferon-beta displayed rapid and widespread distribution in both rats and cynomolgus monkeys.[15] Similar distributions in rats and cynomolgus monkeys were shown – cynomolgus monkeys are primates, and are more closely related to humans.[15] The similarity between the distribution of the drugs in these species provides evidence of the ease in which preclinical results may be translated for use in the clinical setting.

In addition, a large portion of the intranasally administered drug is often lost and is not delivered to the brain.[16,17] However, despite this, this approach seems to show therapeutic benefit with potent drugs.[16] Furthermore, IDDS does not overcome the effect of the efflux transporters, so a drug that is a substrate for p-gp may still be removed from the brain.[19] However, to avoid drug efflux transporters, non-substrate or modified drugs may be used.[19] Additionally, there are local side-effects such as nasal irritation, loss of cilia, and permanent damage to the area.[17]

Discussion

Many DDSs have been developed to overcome the challenges posed by the BBB to pharmacotherapy of the brain.[5] The IDDS presents a promising approach for the delivery of therapeutic proteins and peptides to the brain.[7] This is due to the connection between the nasal cavity and the brain, allowing drugs to be locally administered.[15] Local administration overcomes unfavourable pharmacokinetics and reduces the side-effects of drugs.[10,18] The resulting rapid and widespread distribution of

intranasally administered drugs in the brain prevents the need for BBB permeability modulation.[16] Furthermore, many drugs do not require significant modulation to be intranasally administered, which is often costly and time-consuming. This also applies to large molecule drugs, due to their effective delivery to the brain by IDDS. The IDDS is relatively safe, however, it lacks specificity for damaged or unhealthy cells and/or tissue; nevertheless, the delivery of targeted drugs may overcome this limitation.

Conclusion and future prospects

The BBB remains an obstacle to the pharmacotherapy of neurological disorders.[5] A multitude of DDSs have been developed to overcome this obstacle, such as drug modification, BBB permeability modification, and bypassing the BBB.[5] The IDDS is the best method to circumvent the BBB and presents a non-invasive, relatively safe, and rapid method to deliver drugs to the brain.[16] The future of research on IDDS should focus on improving the correlation between preclinical and clinical settings to aid in the translation of results.[15] Furthermore, a better understanding of the mechanism of drug transport into the brain may allow researchers to better predict which pathway (trigeminal or olfactory) a drug may follow.

Conflict of interest

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