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Extended Abstract

Nanomedicine & Drug Delivery : New biocompatible oxide nanoparticles as carriers of bioactive compounds through the blood-brain barrier- Michal M Godlewski- Warsaw University of Life Sciences

Michal M Godlewski

Abstract

Blood-brain barrier is major obstacle for drug delivery to the brain. In this study, we focused on oxide Nano Particles (NPs) as potential drug carriers. Mice received suspension of Y2O3:Tb:Lectin NPs (10 mg/ml; 0.3 ml/mouse) via gastric gavage (IG) and were sacrificed after 24 hr, 48 hr and 1 week. Control group received equivalent suspension of pure lectin. All protocols were conducted according to EU guidelines and approved by LEC agreement no. 44/2012. Following the sacrifice, brain tissue was collected for the analyses under confocal microscope and scanning cytometry. Lectins were chosen as a perfect model substance for the use of NPs as carriers, since physiologically they are not absorbed from the gastrointestinal tract. Control group exhibited extremely low signal for lectin not exceeding background level. In the group which received Y2O3:Tb:Lectin, signal for lectin coincided with NPs red fluorescence in the brain as soon as 24 hr after IG. Following 48 hours, the convergence lowered and after 1-week only free lectin was observed in the brain tissue. In conclusion, oxide NPs proved able to transport bioactive compounds through the blood-brain barrier. After entering brain tissue complexes of nanoparticles and lectin dissolved and free lectin was deposited in the tissue.

The brain is a highly sensitive and fragile neuronal organ system that needs a regular supply of fuels, gases, and nutrients to maintain homeostasis and other vital functions. But BBB a vasculature of the central nervous system acts as a physical barrier and imposes various obstacles. It inhibits delivery of therapeutic agents to the CNS and imposes obstruction for delivery of large number of drugs, including antibiotics, antineoplastic agents, and neuropeptides, to pass through the endothelial capillaries to brain. Though several drug delivery methods and strategies have been developed for CNS related disease therapeutics, most of them are proved invasive and lack the target specificity. More exceptionally, all traditional drug delivery methods are based on trials and errors. These are applied invariably for delivery of few selected drugs that had appropriate structure-activity relationships or drug-receptor interactions, and its structure-transport relationships are intact. However, maintaining normal body functions and transport of various biological substances including therapeutic agents across biological membranes is highly essential . Only few of the existing methods allow drugs for suitable and successful membrane permeation. Moreover, new drug delivery methods are developed based on rational drug design and using high throughput screening receptor-ligand interactions to find appropriateness of the drug among thousands of new compounds. Further, to reduce the postdelivery toxicity of the drugs noninvasive and less toxic drugs and delivery methods have been developed. Hence, a drug should not be selected only after finding high binding affinity to the receptor, in throughput screening, but it must be found suitable on the basis of structure-activity relationships, target receptor binding, and its behavior in animal system. Though it is possible that it may show invariably poor membrane permeation properties in vivo, such drugs will undergo insignificant transport through the brain capillary endothelium, which makes up the blood brain barrier (BBB) in vivo.

There are so many factors, which influence the drug delivery or its ability to traverse the blood brain barrier. Hence, it is possible that drug may bind to nontransporters in larger amount which render the drug ineffective. Second it seems theoretically/falsely active but really it might show the inability to pass through the blood brain barrier with the adhered protein. Therefore, such drugs cannot be made available to the brain because they cannot be transported and delivered across the blood brain barrier. Further, enzyme action also makes the drug inactive or converts it in a nontherapeutic intermediate compound. However, due to solubility reasons membrane barriers disallow larger molecules while smaller molecules are carried over to the brain. Similarly, charged molecules rapidly get into the brain . Therefore, lipophilicity does not seem to be necessary or lonely factor that may assist the drug for safe passage to brain. However, there seems to be a role of multiple factors or complex molecular properties that make drug able to pass through the BBB. More exceptionally, barrier permeability is also related to membrane or luminal surface of brain capillary, composition of CSF or ISF, functional groups, and change on molecular and ionic surfaces, or presence of charged residues of the molecules. In addition, surface activity of the molecules and its relative size and specific binding of transporter proteins and energy driven cassettes and opening and closing of ion channels due to ionic concentration are key

Michal M Godlewski
Warsaw University of Life Sciences, Poland E-mail: mickgodl@hotmail.com

factors which play an important role in drug delivery .

BBB is nonselective to pass drugs by diffusion or by active transport and creates major hurdles for successful CNS drug development. But it is true that molecules like glucose and fat/lipid soluble drugs can rapidly cross into the brain. Contrary to this, delivery of many of the drug types is very difficult to carry them into the brain because of fat insoluble nature. Besides poor membrane permeation properties, insignificant transport occurs through the brain capillary endothelium affecting the drug availability in theoretically relevant concentration. Major reasons of therapeutic failures are slower drug action, lesser absorption in neuronal and other brain cells, conversion of drug molecule into noninteracting metabolite, and association of drug molecule to other ligands mainly proteins which are nontransporting in nature. Though drug remains therapeutically available in biological system, it becomes ineffective or attains some active molecular form or convert in to a highly reactive molecular state in the brain. This is the main reason why when drug passes through the barrier it might adhere to the unwanted protein in larger amounts. Further, problem may be created by presence of some catabolic enzymes that occur in the brain tissues, which could change the native form of the drug or cleave it into an inactive molecule. There is a possibility that an active drug may change into a slow acting drug molecule that may destructed once it gets inside the brain tissue or enzyme catalytic activity rendering it useless. Therefore, active penetration, structure-activity protection, availability, dispersion, and action of drug in target area are highly needed for the treatment of various CNS disorders and diseases. Further, drug-neuronal receptor interactions, structure-activity relationships, and structure-transport relationships; that is, membrane permeation, must be evaluated for delivery of any drug into the brain.

However, several approaches for direct drug delivery or direct convection-enhanced delivery are used to inject the drug into brain or cerebrospinal fluid or intranasal delivery. These techniques are highly unsafe, invasive local, and metabolizable or short lasting. Contrary to this, there are safe methods which deliver the drug through vascular route which infuse and spread in larger portion of the brain. Hence, for therapeutic purposes active transfer of drug is highly needed. For this purpose safer disruption of BBB or its loosening is highly important to deliver the drug into the brain. Therefore, for successful delivery of drugs, blood brain barrier disruption or opening is done by ultrasound and largely used as intra-arterial infusion therapy. It allows both the chemotherapeutic agents and antibodies to enter through blood brain barrier. Hence, BBB dysfunction could be of great therapeutic value in conditions in which neuronal damage is secondary or exacerbated by BBB damage. However, for therapeutic purposes BBB can be forcibly broken down or disrupted by ultrasonic sound waves for safe delivery of drugs or any therapeutic agent to CNS. But this forced opening may lay structural damage to the BBB and allows the uncontrolled passage of drugs. Further, it is well known that in several areas of the brain BBB is very thin or supposed to be loose or weak, from where drug can easily pass to the brain. These areas also allow passage of important metabolic substances more freely into the brain. These are identified in Pineal body, neurohypophysis, and area postrema. Therefore, by reducing, halting, or reversing the structure and function of BBB new methods can be developed for delivery of chemotherapeutic agents in case of brain tumor. However, in all circumstances both drug composition and its delivery methods must be accounted for making effective drug formulations to treat the CNS disease.

So far many different drug delivery methods have been developed. Few of them are delivered neurologically invasive and found unsafe for drug delivery. These are neurological direct injections or structural disruption of BBB by using ultrasound. Other methods which show broad spectrum and deliver wide range of drugs to CNS are pharmacological and physiological methods which are quite safe and noninvasive. More specifically neurosurgical strategies include BBB disruption by osmotic imbalance or by using vasoactive compounds, intraventricular drug infusion, and intracerebral implants. In pharmacological methods lipid carrier or liposomes are used for drug delivery. Physiological strategies are followed by applying endogenous transport mechanisms by using either carrier mediated transport of nutrients or receptor mediated transport of peptides. From clinical investigations physiological strategies are proved better and potential delivery methods, because of wider safety cover provided by drug transport. Further, conventional strategies should be improved for safe delivery of different drugs to CNS. These include liposomes, colloidal drug carriers, micelles, chimeric peptide technology, intranasal and olfactory route of administration, and nanotechnology. More specifically, nanoenabled delivery systems offer a promising solution to improve the uptake and targeted delivery of the drugs into the brain.

Moreover, brain possesses two drug passing routes for transportation of substances; one is axonal transport that ranges from 20–400 mm/day to a slower 0.1–4 mm/day. It is considered to be a slow route whereby an agent enters the olfactory neuron via endocytotic or pinocytotic mechanisms and travels to the olfactory bulb by utilizing the same anterograde axonal transport mechanisms. Cell uses transport endogenous substances to the brain by this mechanism. The epithelial pathway is a significantly faster route for direct nose-

to-brain transfer, whereby compounds pass paracellularly across the olfactory epithelium into the perineural space, which is continuous with the subarachnoid space and in direct contact with the CSF. Then the molecules can diffuse into the brain tissue or will be cleared by the CSF flow into the lymphatic vessels and subsequently into the systemic circulation. Similarly, nasal spray method could increase the quantity of VIP(vasoactive intestinal peptide) entering the brain and protect the central nervous system. Hence, drugs sent through intranasal route cause minor irritation, which resolve spontaneously within a week at the end of the treatment. More often, intranasal delivery is a noninvasive, safe and alternative approach which rapidly targets delivery of molecules to the brain while minimizing systemic exposure

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Nanoparticles are nanoscale sized polymeric particles which are made up of natural or artificial polymers. These are ranging in size between about 10 and 1000 nm (1 mm). These interact with biological barriers and easily pass through it and are used for drug targeting and biodistribution of pharmaceuticals in a controlled manner. Drugs can bound in form of a solid solution or dispersion or adsorbed to the surface or chemically attached on nanoparticles support carrier loading. Further, polymer used in construction of nanoparticles improves their stability in the biological environment. It also assist to mediate the biodistribution of active compounds, drug loading, drug targeting, transport, release, and interaction with biological barriers. But in normal cases use of nanopolymers is proved to be invasive and toxic as their degradation products create serious problems in the CNS. However, cytotoxicity generated by nanoparticles or their degradation products remain a major problem in drug development. However, valid improvements in biocompatibility are much needed; hence it should be the main concern of future pharmaceutical research

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Michal M Godlewski
Warsaw University of Life Sciences, Poland E-mail: mickgodl@hotmail.com