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A REVIEW ON THE NOVEL MIND TECHNIQUE FOR TREATING NEURODEGENERATIVE DISORDERS

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ABSTRACT

The treatment for neurodegenerative disorders is still a challenge due to presence of the blood– brain barrier (BBB) which limits drug penetration and the intricate and complex pathophysiology of brain disorders. However, in the recent times the intranasal route for drug delivery directly to the brain has strategically been manipulated. Intranasal route of transportation can directly deliver the drugs to brain without the need for systemic absorption, thus avoiding the side effects and enhancing the efficacy of the drugs. The intranasal route although quite promising lacks in translational potential. This review describes the Minimally Invasive Nasal Device (MIND) technique, a novel Nasal to Brain (N2B) drug delivery technique which is designed to overcome inherent anatomical and physiological challenges faced by traditional trans-nasal technique and also facilitates more efficient and targeted drug delivery to treat neurodegenerative disorders. This technique has proved to be successful in providing high CNS uptake and brain distribution of blood-brain barrier (BBB) impermeable drugs via direct administration to the olfactory submucosal space in animal model. The MIND technique can easily be carried out on patients in Ear, Nose and Throat (ENT) clinics, and research suggests that there is significant translational potential of this novel, minimally invasive strategy into a reliable therapeutic delivery approach for the treatment of neurodegenerative disorders.

KEYWORDS: CNS drug delivery, Trans-nasal delivery, Neurodegenerative disease, AntagoNAT, Brain Derived Neurotrophic Factor.

INTRODUCTION

Neurodegenerative Diseases

Neurodegenerative diseases are a group of disorders that are characterized by the progressive degeneration of the structure and function of the central nervous system and peripheral nervous system. Alzheimer's and Parkinson's disease are the two major neurodegenerative diseases that affect millions of people worldwide.[1] The geriatric population has increased in recent years hence causing an increase in age dependent disorders like Alzheimer's and Parkinson's.[2] These diseases primarily affect the neurons in the brain and pose a major threat to human health. Neurons are the building blocks of the nervous system which includes the brain and spinal cord. Neurons are special types cells that allow the brain to communicate with the rest of the body. When these neurons become damaged it leads to death of the neurons, hence there is a loss of brain activity causing problems related to movement or mental functioning. Like other cells of the body, neurons normally don't reproduce or replace themselves, so when they become damaged or die, they cannot be replaced by the body. Hence neurodegenerative diseases are debilitating conditions that result in progressive degeneration or death of nerve cells causing problems with movement (ataxias), mental functioning (dementias) and affect a person's ability to move, speak and breathe. Although treatments and medications may help relieve some of the physical or mental symptoms associated with neurodegenerative diseases, there is currently no way to slow down the progression of this disease and no cure known yet. According to scientists, the combination of a person's genes and environment contributes to their risk of developing a neurodegenerative disease. That is, a person could have a gene that makes them more susceptible to a certain neurodegenerative disease. However, when, and how severely the person is affected depends on environmental exposures throughout life. AD is clinically manifested by progressive impairment in cognition, learning ability, memory function, and executive reasoning.[1] PD is characterized by motor symptoms like bradykinesia, rigidity, resting tremors and postural instability at a more advance stage. They may also be coupled with non-motor features, such as dementia, depression, and autonomic dysfunctions. There is an urgent need to develop new and more effective therapeutic strategies to combat these devastating diseases.[3]

Pathophysiology of Alzheimer's disease

Alzheimer's disease is the most common cause of dementia or memory loss and characterized by cognitive impairment.[4] It causes degeneration of neurons in the brain particularly in the

cortex which leads to symptoms characteristic of dementia. The pathological cause of Alzheimer's is considered to be senile plaques formed due to amyloid beta and neurofibrillary tangles formed due to tau protein. These are plaques and tangles.[5] Amyloid precursor proteins (APP) are trans-membrane proteins.[6] One end of this protein being inside the cell membrane and one end outside the cell. The end outside the cell helps the neuron in growth and repair after an injury. Since APP is a protein, it gets used up and broken down. Under normal conditions it gets broken-down by enzyme called alpha secretase along with another enzyme called gamma secretase. The protein part chopped by these two enzymes is soluble and hence no issues are faced. However, if another enzyme called beta secretase instead of gamma secretase takes part in breakdown with alpha secretase it leads to formation of protein fragments that are insoluble. This ends up creating a monomer called Amyloid Beta. These monomers accumulate and end up forming clusters just outside of neurons known as Beta Amyloid Plaques and are considered to be responsible for neuronal and vascular degeneration in AD patients.[7] These plaques can get between the neurons which gets in the way of neuron-to neuron signalling. If the brain cells can't signal and relay information then brain functions can become seriously impaired. These plaques can also cause inflammation which might damage the surrounding neurons. Amyloid beta found in senile plaques is considered to be the initiating factor in pathology of Alzheimer's disease.[8-9] Another cause of Alzheimer's is formation of neuro fibrillary tangles which are found inside the cells. Neurons are held together by their cytoskeleton which is partly made up of microtubules. Tau is a special microtubule- associated protein helps in keeping the microtubules intact.[10] The tau protein functions to help maintain microtubule structure and cytoplasmic transport function.[11] It also plays an important role in neuronal signalling.[12] It is thought that the beta amyloid plaque build-up outside the neuron initiates pathways inside the neuron which leads to the activation of kinase enzyme, that causes the phosphorylation of tau protein. The tau protein then changes shape, stops supporting the microtubules and clumps with other tau proteins and gets tangled. The aggregation of tau proteins is very closely related to cognitive decline and brain atrophy.[13] This leads to other characteristic finding of Alzheimer's disease that is neurofibrillary tangles. Hyper phosphorylated Tau proteins in Alzheimer's patients' brains causes configuration changes and the loss of tubulin polymerization capacity, resulting in defective microtubule functioning.[14] Neurons with tangles and non-functioning microtubules are unable to single properly and hence end up undergoing apoptosis or programmed cell death.

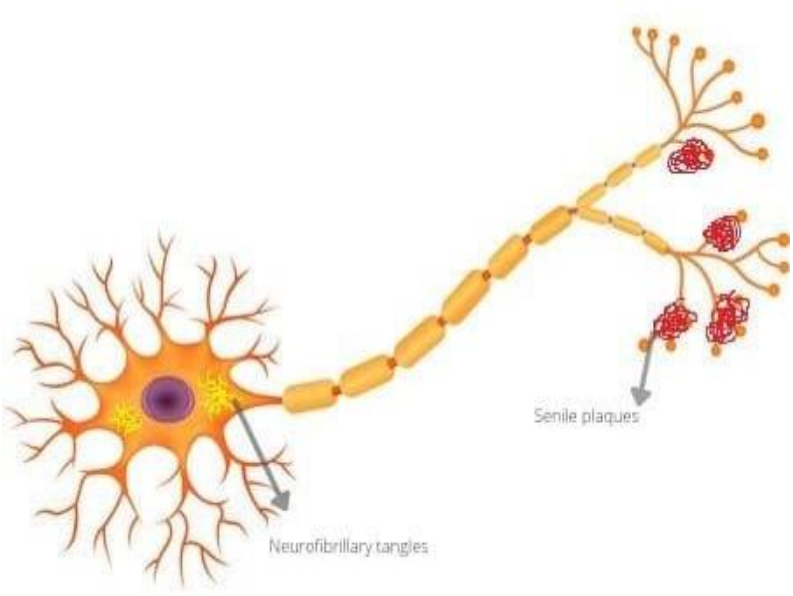


Figure 1: Neurofibrillary tangles and senile plaques seen in Alzheimer's brain.

As neurons start to die, large scale changes start to take place in the brain. The brain atrophies or shrinks and the Gyri become narrower which are the characteristic ridges of the brain. The Sulci which are the grooves between the Gyri get wider. With atrophy the ventricles that are fluid filled cavities in the brain get larger as well.

Pathophysiology of Parkinson's Disease

Parkinson's disease is a progressive neurodegenerative disorder in which the dopamine producing neurons of a brain structure called substantia nigra are damaged and die over time leading to a number of motor problems and mental disabilities.[15] Parkinson's disease can be identified by two considerable pathological processes that is early selective loss of dopamine neurons and formation of Lewy bodies made up of alpha synuclein.[16] Substantia nigra is a part of the basal ganglia whose major function is to inhibit unwanted motor activities. When a person wants to make movement, this inhibition is removed by the action of dopamine. As dopaminergic neurons are progressively lost in Parkinson's patients, low levels of dopamine make it harder to initiate voluntary movements. this makes PD a neurological disorder in which movement is affected.[17] Resting tremors, rigidity, bradykinesia, decline in balance and motor coordination, slow movements and problems relate with gait and speed are all movement related symptoms of PD.[18] Other motor related problems include slurred speech, and reduced facial expressions. The events leading to neuronal cell death are not yet fully understood but the presence of Lewy bodies is found to be the reason as it is found in neurons

before they die. Lewy bodies are fibrillar aggregates composed majorly of alpha synuclein.[19] They are alpha-synuclein-immunoreactive inclusions made up of a number of neurofilament proteins together with proteins responsible for proteolysis. Mutations in the alpha-synuclein gene are responsible for some familial forms of PD in which Lewy bodies are also see.[20] Accumulation of Lewy bodies leads a loss of certain neurons in the brain that produce two important neurotransmitters. One of these messengers is acetylcholine which is important for memory and learning. The other is dopamine which plays an important role in behavior, cognition, movement, motivation, sleep, and mood. An imbalance between the inhibitory dopaminergic and excitatory cholinergic system in the striatum occurs which leads to a motor defect. Though the cholinergic system is not primarily affected, its suppression tends to restore balance. The symptoms of Parkinson's develop slowly over time. Non motor symptoms such as mood and behavioral changes, cognitive impairment and sleep disturbances may also be observed in Parkinson's patients.

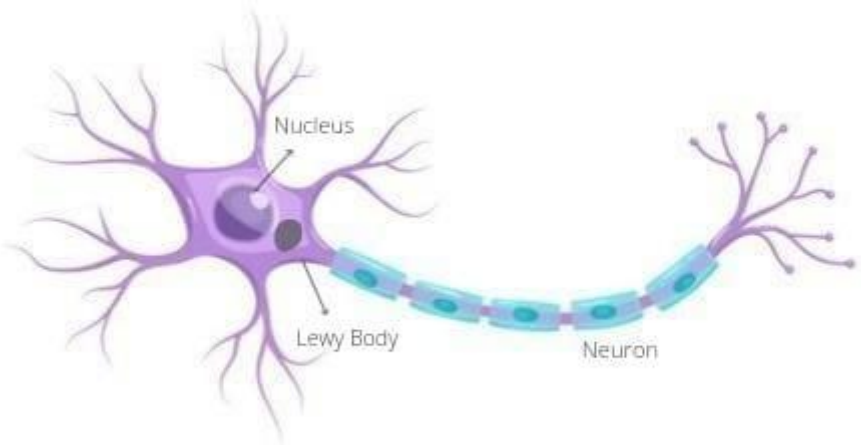


Figure 2: Lewy bodies found in neurons in Parkinson's patient.

Shortcomings of oral route

The low bioavailability and limited brain exposure of oral drugs, the rapid metabolism, elimination and the unwanted side effects are just some of the downsides of using oral routes for drug delivery. Also, the high dose to be added cause inconvenience for the patients by increasing the cost for the patients. Due to the presence of the BBB some drug compounds have low penetration however intranasal drug administration can bypass the BBB which makes it a promising approach. This way the dose administered can also be lowered which in turn may also lead to reduced systemic adverse effects. Intranasal drug delivery also does not require any modification of the therapeutic agent being delivered like converting the drug

into a prodrug. It gives rapid onset of action and is also found to be patient compliant. It can work for a wide range of drugs and especially facilitate the treatment of many CNS disorders. The rich vasculature and highly permeable structure of the nasal mucosa greatly enhance drug absorption and also the easy access to blood capillaries is one of the prime advantages of N2B delivery. Problem of degradation of peptide drugs is minimized up to a certain extent and hepatic "first pass metabolism" is also avoided allowing increased bioavailability.[21–26]

ANATOMY AND PATHWAYS FOR NASAL DRUG DELIVERY

Olfactory nerve pathway

In order for a drug to travel from the olfactory region in the nasal cavity to the CSF or brain parenchyma, it has to travel through the nasal olfactory epithelium and, depending on the pathway followed one can envisage three different pathways across the olfactory epithelium.

1) Transcellular pathway

This takes place especially across the unspectacular cells either by receptor-mediated endocytosis, fluid phase endocytosis or by passive diffusion. Lipophilic drugs usually traverse through passive diffusion. Passive diffusion is rapidly mediated and at a high rate. This route is responsible for the transport of lipophilic drugs and it shows rate dependency based on the lipophilicity of the drug.[27,28]

2) Paracellular pathway

In nasal epithelium, the cells are connected with each other via different junctions like tight junction, zonula adherens and macular adherens.[29] These junctions are impermeable to large molecule drugs but due to continuous turnover of neuronal and basal cells become permeable and closing of these junctions promotes the paracellular transport.[30] Nasal absorption of hydrophilic drugs mostly occurs by diffusion through aqueous channels (pores). This pathway is slow and passive. This route is responsible for transport of hydrophilic drugs and the rate of transport also depends on the molecular weight of a drug. Drugs with molecular weight up to 1000 Da can travel across without absorption enhancer and also shows good bioavailability. Drugs with molecular weight up to 6000 Da would need an absorption enhancer to traverse.

3) The olfactory nerve pathway

This pathway plays a vital role in drug delivery via N2B and consists of olfactory epithelium, lamina propria and olfactory bulb. Olfactory epithelium contains three types of cells and they

are neuronal cell, supporting cells and progenitor cells. All these cells are connected through tight junctions. Neuronal cells stretch from olfactory bulb in CNS to olfactory epithelium in nasal cavity and pass on information to the brain. Basal cells and neural cells replace each other during their constant motion and due to this constant motion and replacement nasal mucosa becomes permeable which results in enhanced drug delivery to the brain. In olfactory nerve pathway the drug is taken up into the neuronal cell by endocytosis or pinocytosis mechanisms and transported by intracellular axonal transport to the olfactory bulb.[31–33]

Trigeminal pathway

Respiratory region occupies major portion of nasal cavity which is innervated by trigeminal nerves. Trigeminal nerve is the largest nerve among all the cranial nerves and it is the fifth (V) cranial nerve having three branches; ophthalmic nerve, maxillary nerve and mandibular nerve. It also happens to be responsible for sensation in nasal cavity. This nerve innervates the respiratory and olfactory epithelium of nasal passages and enters the CNS in the pons. A minute portion of trigeminal nerve also ends in the olfactory bulbs. The trigeminal nerve communicates sensory information from the nasal cavity to the CNS. The trigeminal nerve enters the brain from the respiratory epithelium at two sites. one is via anterior lacerated foramen near the pons and the other is through the cribriform plate near olfactory bulb, creating entry points into both caudal and rostral brain areas following intranasal administration.[34-35]

BARRIERS TO NASAL DRUG DELIVERY

Blood brain barrier

The blood-brain barrier (BBB) is formed by brain capillary endothelial cells (ECs).[36] It refers to the highly selective permeability of blood vessels within the central nervous system. The barrier controls substances that can enter or leave the nervous tissue in a precise manner and helps in maintaining homeostasis of brain tissue. The BBB has an insulating function which restricts access to brain of many natural toxins, antibodies, and biologic complexes.[37] It helps to protect the brain from blood borne pathogens and toxins. The BBB significantly stops entry of virtually all molecules, from blood to brain, except those that are small and lipophilic. However, small hydrophilic molecules can enter the brain, by active transport.[38] The “gatekeeper” to the brain, BBB determines the ability of drugs to gain access to brain extracellular fluid and reach therapeutic concentrations within the CNS.[39-40] Neural cells namely pericytes partially cover the outside of endothelial cells and glial cells astrocytes

whose extended process wrap around the vessels. The endothelial cells alone can fulfil the functions of the BBB but their interactions with the adjacent cells seem to be required for its formation, maintenance and regulation. The brain endothelial cells possess unique properties that allow them to tightly control the passage of substances between the blood and brain. and allow vesicle mediated transcellular transport at a very low rate. They control the movement of ions and substances with specific transporters of which there are two major types efflux transporters and nutrient transporters. Efflux transporters use cellular energy to move substances against their concentration gradient and these are located on the blood side of endothelial cells. Their main function is to transport back lipophilic drug molecules that have passively diffused through cell membrane to blood nutrient transporters. On the other hand, nutrient transporters facilitate the movement of nutrients such as glucose and essential amino acids into the brain down their concentration gradient. The brain endothelial cells also contain a number of enzymes that metabolize and thus inactivate certain neurotransmitters, drugs and toxins preventing them from entering the brain. Neurological diseases such as Alzheimer's disease, epilepsy, strokes and tumors can breach the barrier and this in turn contributes to disease pathology and further progression. However not all areas of the brain have the blood brain barrier for example some brain structures are involved in hormonal control and require better access to systemic blood so they can detect changes in circulating signals and give response accordingly. These nonbarrier areas are known as circumventricular organs. Some of the regions of circumventricular organs have a leaky barrier. the blood brain barrier also has its downside while it protects the brain from unwanted drugs and toxins it also prevents therapeutic drugs from entering the central nervous system to treat diseases. Several strategies have been implemented to manipulate these sites to deliver drugs to CNS via BBB.

Brain Cerebrospinal Fluid

Cerebrospinal fluid is a colorless liquid that protects the brain and spinal cord from physical and chemical damage. It circulates through the ventricles of the brain, the subarachnoid space and the central canal of the spinal cord. Cerebrospinal fluid is a part of extracellular fluid, and it contains various substances which are both organic and inorganic. It also contains lymphocytes. The total volume of cerebral spinal fluid in a healthy adult is between 80 to 150 milliliters.[41] There are three main functions of cerebrospinal fluid and the first one is to provide a suitable chemical environment for neuronal signaling. The balance of positive and negatively charged ions help in the production of action potentials and postsynaptic potentials. If this balance is disrupted, the production of the nerve potentials can seriously

disrupt. It also functions as a shock absorbing medium, it helps by protecting the delicate tissues of the brain and the spinal cord from sudden jerky movements. It is also involved in the exchange of nutrients and waste between the blood and nerve tissue.[42] There are four cerebral spinal fluid filled cavities in the brain and they're called ventricles. There is a lateral ventricle in each hemisphere and these lateral ventricles are separated by a thin membrane called septum pellucida. Cerebrospinal fluid is produced in the choroid plexus, which are capillary networks found in the walls of the third and the fourth ventricles. It's the ependymal cells of these capillaries which form the cerebrospinal fluid by filtration of blood plasma. Components to be filtered to form cerebrospinal fluid don't leak backwards because of the tight junctions between these choroid plexus cells. This is called the blood cerebrospinal fluid barrier, which allows certain substances to pass through to cerebral spinal fluid but not others. This is a way of protecting the brain and reducing the risk of contamination.[43]

Minimally Invasive Nasal Depot

Owing to the limitations that are faced during topical intranasal delivery of large drug molecules for CNS disorders like high dose variability, poor bioavailability and blood brain barrier a concept of Minimally Invasive Nasal Depot was established. It is a novel method for direct trans nasal CNS drug delivery which delivers the entire therapeutic dose directly to the olfactory submucosal space and also overcomes the challenges faced by topical intranasal drug delivery. Implantation of a depot containing an AntagoNAT(AT) is capable of derepressing the Brain Derived Neurotrophic Factors (BDNF) expression which is enabled by CNS distribution of ATs with significant and sustained up regulation of BDNF. The efficiency of this technique approaches 40% of ICV delivery in this technique. The drug depot is directly injected to the submucosal space of olfactory epithelium, facilitating its direct CNS delivery. The idea of minimally invasive nasal depot technique is based on routine Intranasal procedures performed by otorhinolaryngologist specialist in Ear, Nose and Throat (ENT) clinics using commonly available endoscopic instrumentation in awake patients with minimal discomfort. In this approach, the drug is suspended in a gel carrier and is directly injected into the submucosal compartment of the olfactory epithelium. In doing so, the entire dose is implanted within the tissue directly surrounding the olfactory neurons, thereby fixing the concerns regarding distribution, retention, transepithelial diffusion and dose uniformity. The MIND technique holds significant translational potential due to the ease and safety of this technique and can be performed in the clinic both on adult and pediatric populations suffering from CNS disorders.[44,45]

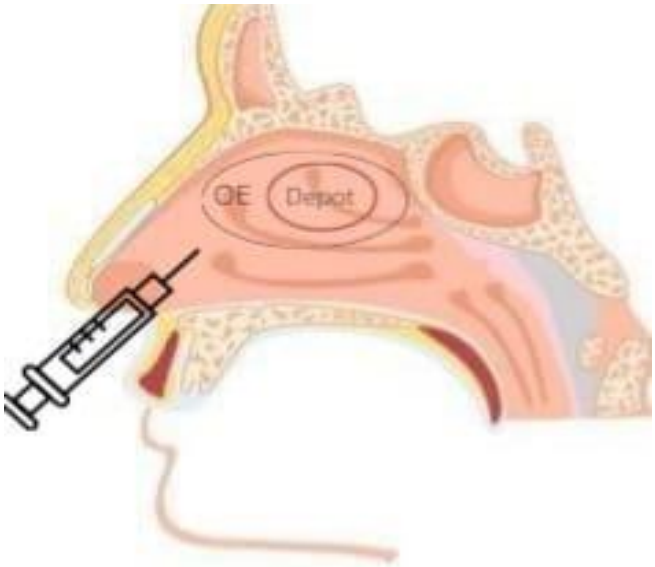


Figure 3: Nasal injection for depot deposition given in Olfactory Epithelium submucosa.

Figure 4: Nasal Endoscopy being performed on a patient.

Brain Derived Neurptrophic Factor

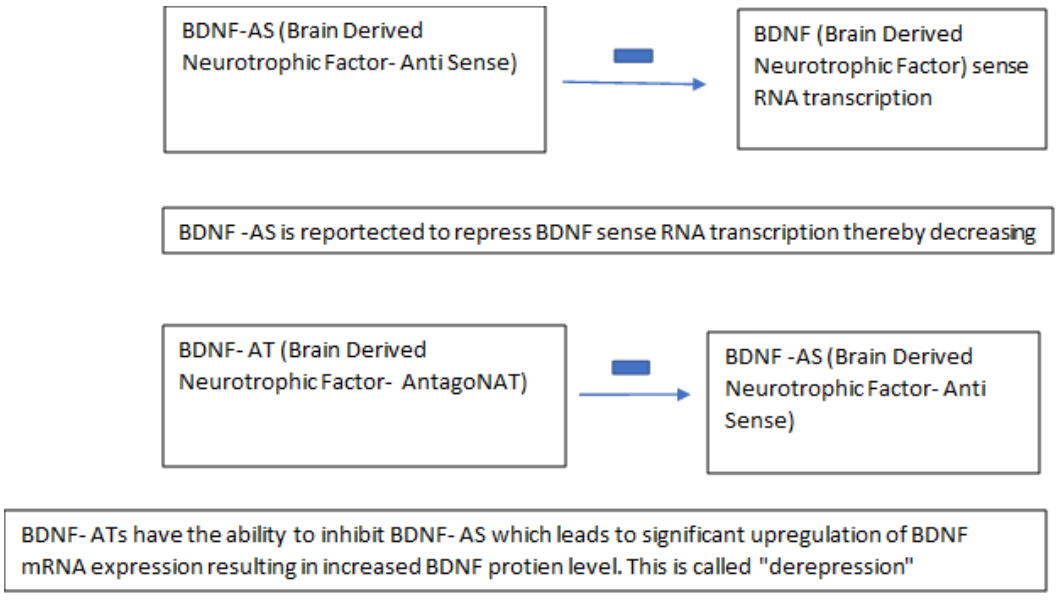
Brain Derived Neurotrophic Factor (BDNF) also known as the brain fertilizer, is a specific gene that relates with a specific protein that grows new neurons and new synapses in our brain. Hence it is the epicenter for growth and development in a human brain. It not only grows new neurons and synapses but it also protects the existing neurons. So, it has both a protective and growth function to play in the brain. Neurotrophic factors are capable of stimulating both prosurvival and pro-functional neuronal activity, which is why they are nowadays being used to treat several neurodegenerative disorders. BDNF has been found to support neuronal survival and differentiation. Also decrease in production of BDNF within the cortex, hippocampus, and substantia nigra has been reported to result in neuronal loss

which can ultimately contribute to neurodegenerative diseases like Alzheimer's and Parkinson's.[46] These findings have led to finding out strategies to increase BDNF levels in an effort to mitigate disease progression in these patients. There are four types of Neurotrophin which play an important role during the nervous system development and neuronal plasticity. Of these, BDNF has the most abundant and widespread expression in the human brain. BDNF is released from both pre and post synaptic neurons.[47] It has a complex structure owing to the presence of 11 different exons which are regulated by 9 different types of functional promoters.[48] It causes cells to generate many BDNF transcripts. Secreted BDNF can interact with two receptors, the p75 neurotrophin receptor (p75NTR) and the tropomyosin related kinase receptor B (TrkB). Signaling by BDNF depends on the proteolytic cleavage of a pro-form of BDNF to mature form, whereas pro form binds preferentially to P-75NTR mediating apoptosis and long-term depression, mature BDNF binds to TrkB and simulates downstream signaling pathways, leading to a plethora of effects like neuronal differentiation, outgrowth of neuron, outgrowth of neurites, increased cell survival, and strengthening of synapses.[49-50] Due to its role in neurogenesis and long-term potentiation, BDNF signalling in the limbic structures and the cerebral cortex is central for learning and memory.[51] Of BDNF signaling in the brain, mainly due to decrease in expression of release has been linked to a range of psychiatric and neurological disorders in the recent years. A polymorphism in the coding region of the pro domain of BDNF called Val66Met is associated with memory impairment in humans.[52-53] Studies suggest that the polymorphism leads to increased BDNF release. BDNF replacement therapy is actively being pursued in human and animal models of diseases including Huntington's disease, Alzheimer's and depression. Furthermore, antidepressant treatment has shown to increase the level of serum BDNF in depressed patients. Due to the central role of BDNF in brain development and plasticity, early environmental factors on BDNF levels may have long term effects on the brain activity.[54-55]

Oligonucleotide based therapies

Oligonucleotide based therapies for treatment of neurodegenerative disorders is gaining importance due to its ability to restore the imbalance of neurotrophic factors in the brain. Antisense oligonucleotides (ASOs) are synthetic single stranded strings of nucleic acids that bind to RNA and cause alterations or decrease the expression of target RNA. They can reduce expression of mutant proteins by breakdown of the targeted transcript, but they can also restore protein expression or modify proteins through interference with pre-mRNA

splicing[56] can alter the gene expression in multiple ways either by blocking translation, altering stability, modifying splicing, or eliciting degradation pathways altering the target mRNA's expression.[57] Natural antisense transcripts (NATs), which are complementary to the corresponding mRNA, are heterogeneous and often accumulated in the nucleus.[58] likely have regulatory functions[59], but their rather modest expression level[60] made it difficult to clearly establish their role. As NAT's which are non-coding RNAs transcribed specifically from the opposite strand of the coding gene are present in abundance in the mammalian genome, oligonucleotidebased therapies can be used effectively. NATs have the ability to regulate their corresponding sense gene expression. For example, BDNF-Antisense (BDNF-AS) was reported to repress BDNF sense RNA transcription by changing the BDNF locus chromatin composition, thereby decreasing the levels of endogenous BDNF protein. Inhibition of BDNF-AS was found to significantly upregulate BDNF mRNA expression resulting in increased BDNF protein levels. This "derepression" can be achieved using AntagoNATs (ATs) which are synthetic, short, chemically modified, single-stranded oligonucleotide-based compounds, complementary to a particular NAT. In particular, BDNF AntagoNAT (BDNF AT) can inhibit BDNF-AS activity. Upregulation of endogenous BDNF by AntagoNATs was found to induce neuronal differentiation and neuronal proliferation. oligonucleotide based therapy is gaining interest, particularly due to high target specificity, reduced systemic exposure, limited toxicity, and relatively prolonged half-life within the CNS as compared to the majority of the small molecule drugs.[44] Moreover, the cells can carry out free uptake of oligonucleotides which mitigates the need to use carriers which might be potentially toxic or immunogenic. this makes OBT a much better therapeutic option.



METHODOLOGY

A study was conducted to reiterate the human MIND technique in healthy Sprague Dawley rats. In humans the olfactory epithelium can directly be accessed using an endoscopically guided trans nasal injection without any need for anesthesia. However, for rats the process is slightly different. As their snout is very small to access the trans nasal space, an open surgical approach was performed to remove the nasal bone which created subcutaneous space for implantation of the depot. The study was conducted on rats for three formulations i.e., BDNF AT-Liposome-in Gel and BDNF AT-in Gel under 7 different time points (2, 6, 12, 24, 48, 72 and 96 h) for investigating the safety and efficacy of MIND technique and the ICV (intracerebroventricular) BDNF AT solution also used 4 rats at 3 time points (2, 12 and 24 h). Levels of drug released from all the three types of formulations in different regions of brain like olfactory bulb (OB), striatum (STR), hippocampus (HC), substantia nigra (SN) and cerebellum (CB) were quantified by hybridization assay. BDNF protein levels were measured by ELISA. Non compartment analysis of concentration and time curves of both AT levels and BDNF protein levels for the three formulations were performed. The results obtained revealed that BDNF protein levels were substantially upregulated in all brain regions for both MIND formulations in comparison to the naïve rat's BDNF levels. There was no significant difference between BDNF levels for both AT-G and LiG formulations at all time points, despite the distinct differences noted in the mean AT concentrations between the two groups. The mean BDNF protein levels in brain tissues of rats dosed with ICV AT were also compared to those of MIND formulations. BDNF was found to be significantly upregulated after AT administration, regardless of route or formulation, as early as 2 h post-administration in different brain regions, especially SN and CB. moreover, CB BDNF levels at 2 h after ICV as well as MIND AT dosing were remarkably higher compared to the levels at other brain subregions. At 12 h, the ICV administration demonstrated higher mean BDNF protein concentrations compared to both MIND formulations. However, the mean BDNF protein levels of all groups were found to be similar at 24 h in brain regions such as OB, STR and CB. however, the mean BDNF protein levels at 24 h, especially after MIND AT-G administration were significantly elevated in HC and SN compared to BDNF values of naïve rats. An efficient CNS uptake and brain distribution of BDNF ATs was attained through MIND delivery which led to significant BDNF upregulation in various brain sub-regions, particularly in hippocampus and substantia nigra, which were relevant areas of interest for the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's. The efficiency

of MIND technique approached 40% of direct ICV delivery which suggests good distribution of drug in the required areas.[44-45]

CONCLUSION

The biggest challenge faced in treatment of neurodegenerative disorders is delivery of drug to the desired site which is hindered by the presence of BBB. MIND technique is an innovative drug delivery system which delivers the desired concentration of drug at the required site by overcoming the obstacles presented by BBB. MIND technique has also proved to be an attractive option for direct nose to brain drug delivery due to its non- invasiveness compared to the ICV delivery. An efficiency approaching 40% of direct ICV delivery is achieved by MIND technique which proves that it is highly effective and can be used as drug delivery strategy for treatment of neurodegenerative disorders.

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