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Neurodegenerative diseases and effective drug delivery: A review of challenges and novel therapeutics

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Abstract

The central nervous system (CNS) encompasses the brain and spinal cord and is considered the processing center and the most vital part of human body. The central nervous system (CNS) barriers are crucial interfaces between the CNS and the periphery. Among all these biological barriers, the blood-brain barrier (BBB) strongly impede hurdle for drug transport to brain. It is a semi-permeable diffusion barrier against the noxious chemicals and harmful substances present in the blood stream and regulates the nutrients delivery to the brain for its proper functioning. Neurological diseases owing to the existence of the BBB and the blood-spinal cord barrier have been terrible and threatening challenges all over the world and can rarely be directly mediated. In

fact, drug delivery to brain remained a challenge in the treatment of neurodegenerative (ND) disorders, for these different approaches have been proposed. Nano-fabricated smart drug delivery systems and implantable drug loaded biomaterials for brain repair are among some of these latest approaches. In current review, modern approaches developed to deal with the challenges associated with transporting drugs to the CNS are included. Recent studies on neural drug discovery and injectable hydrogels provide a potential new treatment option for neurological disorders. Moreover, induced pluripotent stem cells used to model ND diseases are discussed to evaluate drug efficacy. These protocols and recent developments will enable discovery of more effective drug delivery systems for brain.

Abbreviation

Ach	Acetylcholine
AD	Alzheimer's disease
ALA	Acellular nerve allograft
ALS	Amyotrophic lateral sclerosis
ANA	Acellular nerve allografts
BBB	Blood brain barrier
B6: CGHKAKGPRK	transferrin-mimetic peptide
BCSFB	Blood cerebrospinal fluid barrier
BTB	Blood tumor barrier
CNS	Central nervous system

CSF	Cerebrospinal fluid
COMT	Catechol O-methyltransferase
CP	Choroid plexus
DDS	Drug delivery system
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
FDA	Food and Drug Administration
HA	Hyaluronic Acid
HAMC	Hyaluronan-methylcellulose
HD	Huntington disease
HP	Huntington ‘s disease
IGF	Insuline growth factor
IPSCs.	Induced pluripotent stem cells
JAMs	Junctional adhesion molecules
LDC	Lipid drug conjugate
MAO inhibitor	Monoamine oxidase inhibitors
NAP	Neuroprotective activity peptide

NAPVSIPQ	Neuroprotective peptide NAP
ND	Neurodegenerative diseases
NLC	Nanostructured lipid carrier
NBDDS	Nano biomaterial drug delivery system
NPSCs	Neural progenitor cells
NPs	Nanoparticles
NSC	Neural stem cells
PD	Parkinson's disease
PEG	Polyethylene glycol
PLA	Polylactic acid
PGA	Poly glycolic acid
PHEMA	Poly (hydroxyethyl methacrylate)
PLLA	Poly (L lactic acid)
PLGA	Poly (lactic-co-glycolic acid)
SLN	Solid lipid nanoparticles
SN	Subtantia nigra
TJ	Tight junction
VEGF	Vascular endothelial growth factor

Keywords

Blood brain barrier, Neurodegenerative diseases, Nanotechnology, Brain targeted drug delivery, Polymer implants, Injectable, Stem cells

Contents

1. Introduction

The delicate organ of the central nervous system (CNS) is brain which interrelates the input from sensory endings in all organ, considers learning and memory, and enables for running repairs to maintain active function [1]. With the aging of the world population, neurological disorders are responsible for contributing 6.3% of the global burden of all diseases. As a consequence, these disorders causes major health issues of disability and are leading to additional medical treatment and prolonged care [2]. The drug delivery through central nervous system is a major challenge although there is relatively a high flow of blood. The series of barriers to protect itself have been emerged by CNS including the blood brain barrier (BBB), blood–cerebrospinal fluid (CSF) barrier, the blood–retinal barrier, and the blood–spinal cord

barrier. The brain from its blood supply is separated by the two physiological barriers, BBB and the blood–cerebrospinal fluid barrier (BCSFB) [3, 4].

Among all the barriers, BBB is the stronger one, which impedes the noxious chemicals and harmful substances from the bloodstream and regulates the nutrients delivery to the brain for normal function. BBB is a semi–permeable and diffusion barrier constructed of astrocytes, endothelial cells, tight junctions, neurons pericytes and basal membrane [5, 6]. Different kinds of transport pathways for the delivery of these substances at the BBB are schematically shown in Fig. 1. These delivery tools work from brain-to-blood direction and blood-to-brain direction modes. However, blood to brain transport system is of more important in drug delivery as compared to the other transport system [2, 7, 8]. Immediately after BBB, another barrier is BCSFB that encounters a systemically regulated drug before going into the CNS. This is located at the choroid plexus that controls the transfer of solutes from blood to CSF and fresh CSF is secreted by it. Choroidal epithelium is a complex organ having many extra functions like neuro-immune and neuroinflammatory responses, drug and toxin metabolism, neuroendocrine signaling, metabolism and transport [9, 10].

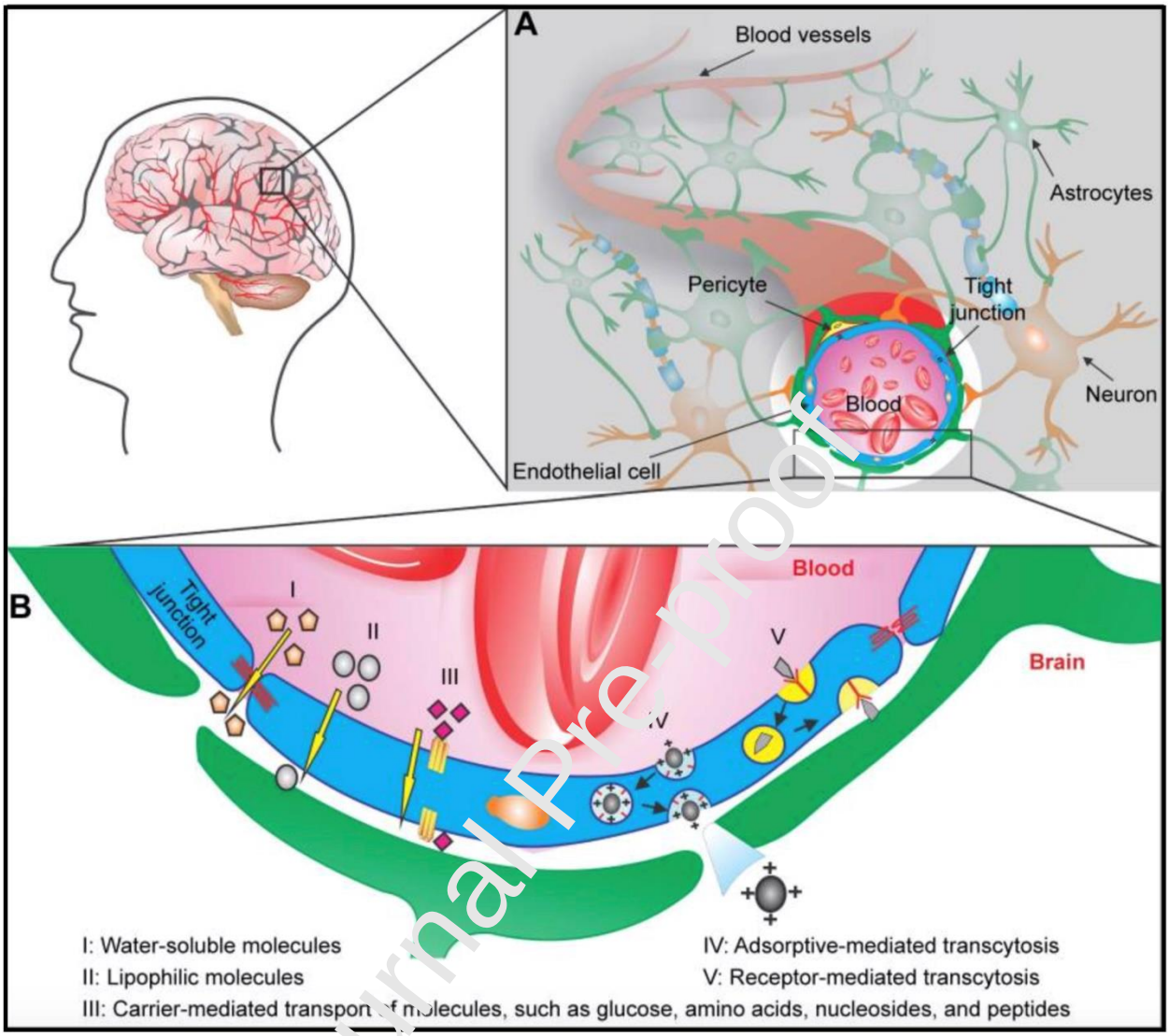

Fig. 1. Channels to pass the blood brain barrier [8]. (Reproduced from an open access source.**)**

The BBB is found at the walls of the blood vessels. (A) Cross section of a cerebral capillary reveals the structure of the BBB having a network of pericytes, neurons, astrocytes and endothelial cells. (B) Different modes of drug release over the BBB. Water soluble molecules go into the BBB (I), lipid-soluble molecules disperse over the endothelial cells (II), carried mediated transport machineries carry out small molecules and peptides (III) ,cationic drug improves its uses by adsorptive-mediated transcytosis (IV) ,larger molecules are brought through receptor-mediated transcytosis (V).

Despite of progresses in disease pathology, there is a limited number of drugs available for neurological disorders. Specifically, drug release to brain remained a major problem in treating neurodegenerative (ND) disorders. In order to overcome these limitations nanotechnology could be very helpful [11-14]. The very small size and very high surface of nanomaterials make distinction between nanoscience and other classical technologies. Presently, nearly all macro molecular drugs and larger than 98% of small drug -molecules have been failed in crossing BBB and drug candidates showed poor biopharmaceutical and pharmacokinetics properties [7]. Therefore, suitable drug delivery systems without disturbing healthy organs and tissues for the distribution of drug molecule are strongly needed. Although nanoparticles administered systemically are chemically more stable but they hold drawbacks associated with the preparation of nanoparticles, specifically the large-scale industrial production and quality control. Furthermore, the safety when injected, and the effect of nanoparticles on the CNS after permeating the BBB need to be further investigated [7, 15, 16]. Implanting therapy and utilization of anticancer drug-loaded biomaterials e.g. hydrogels are the modern treatment options for the ND diseases [17, 18].

This review highlights and discusses the fundamental functions of the BBB, limitations of the application of nanoparticles-based drug release systems, considering the most common ND diseases and recent advances in latest injectable implanted drug loaded biomaterials used to promote brain repair.

2. Barriers to drug delivery

The drug release to the CNS through the cardiovascular system is impeded by different distinct barriers such as BBB, Blood-Cerebrospinal Fluid Barrier (BCB), and Blood-Tumor Barrier (BTB). In the current article we review the details of such barriers.

2.1 Blood-brain barrier

Blood-Brain Barrier (BBB) is composed of the brain capillary endothelial cells, which includes astrocytes and pericytes as the major components and schematically shown in Fig. 2 [10, 19]. BBB is a permeable barrier that permits proteins, enzymes and nutrients entry and restricts water-soluble substances. Thus, it restricts entry of drugs, therapeutic and diagnostic agents during treatment of ND disorders. [20-22].

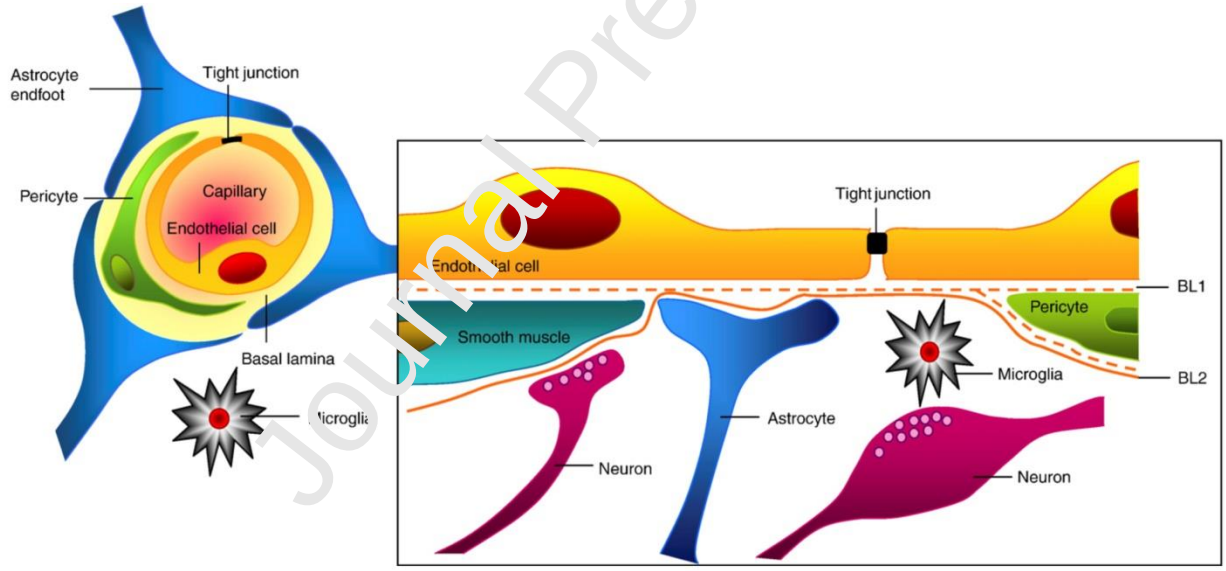

Fig. 2. Various components of the blood–brain barrier [10]. (Reproduced with permission from journal.)

The cerebral endothelial cells form tight junctions at their margins and seal the aqueous paracellular diffusional route between the cells. Pericytes partially surround the endothelium and

are spread nonuniformly besides of the cerebral capillaries. The cerebral endothelial cells and the pericytes both together contribute to and are surrounded by, the local basement membrane BL1, vary in constitution from the extracellular matrix of the glial end feet (BL2). Foot operations from astrocytes configure a complex network surrounding the capillaries and this close cell union is significant in maintaining the barrier properties. The delivery of vasoactive peptides regulates the permeability of BBB. The motion of solutes over the BBB may be facilitated by passive or active carriers in the endothelial cell membranes or is passive, with more lipid-soluble substances.

2.2 Blood-cerebrospinal fluid barrier BCSFB

BCB experiences systemically operated therapeutic drug before going into the CNS. Cerebrospinal-fluid (CSF) can interchange molecules with the interstitial fluid of the brain parenchyma and carefully regulate the passage of blood-borne molecules into the CSF. This is located in the epithelium of the choroid's plexus that comprises a highly vascularized stroma having connective tissue and choroidal epithelial cells. CP is found besides of the lateral, third, and fourth ventricles of the brain. CP also configures an interface between cerebrospinal fluid (CSF) and peripheral blood and may form more than 50% of total CSF. The principal purpose of the CP is to produce. BCSF and the CSF barrier, besides that the CP might be the part of the circadian regulatory system. The choroid's plexus behaves as a physical, immunological and enzymatic barrier which assists the drug transport, metabolism and signaling functions and restricts transport into the CSF as well [23-26]. The choroid plexus vigorously regulates the concentration of molecules in the CSF and the various transfer and secretion channels operative in the choroid plexus epithelial cells, make them suitable to control the molecular and cellular composition

brain fluid and CSF and with the arachnoid membrane, performs between the blood and CSF at the barriers [25, 27, 28]. Thus therapeutic organic acids are actively taken out from the CSF [29, 30].

2.3 Blood-tumor barrier

Intracranial drug delivery becomes more difficult in case of CNS tumors. BBB shows clinical outcomes in the microvasculature of CNS tumors. The physiological barriers impede drug delivery via the cardiovascular system in CNS malignancies. Approaches such as inhibiting efflux drug transporters, opening TJs by a hyperosmotic solution of mannitol and receptor-mediated drug delivery systems may also be utilized facilitating drug through it [6, 31, 32]. Fig. 3 exhibits the central nervous system barriers. Whereas schematic representation of blood brain barriers is depicted in Fig 4 [33, 34].

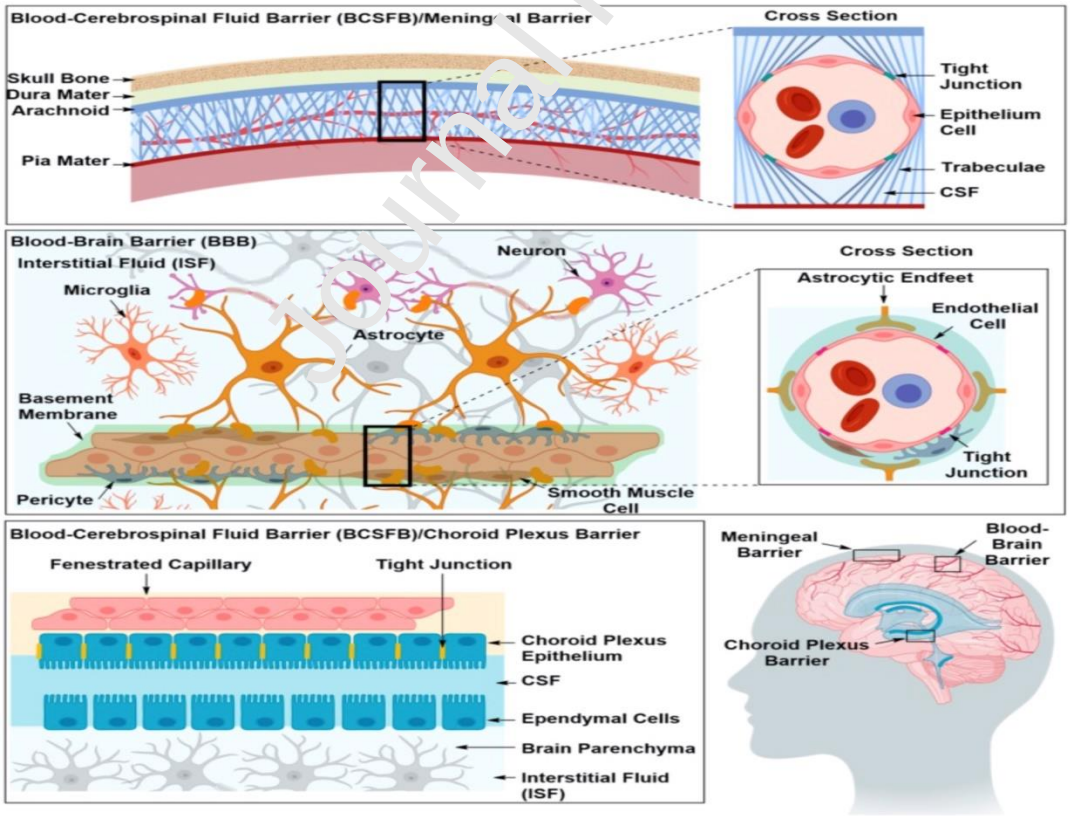

Fig. 3. The three main barriers in the central nervous system (CNS) [33]. (Reproduced with permission.)

The meningeal or arachnoid barrier, the choroid plexus barrier and the blood brain barrier (BBB) are the three main barriers in the central nervous system (CNS).The blood from the cerebrospinal fluid (CSF) is separated by the arachnoid and choroid plexus barriers and the BBB separates the blood from the interstitial fluid (ISF).The blood brain barrier owns an intricate architecture of mural, glial cells and basement membrane that altogether are responsible for the maintenance the barrier's integrity and regulate its permeabil ty.

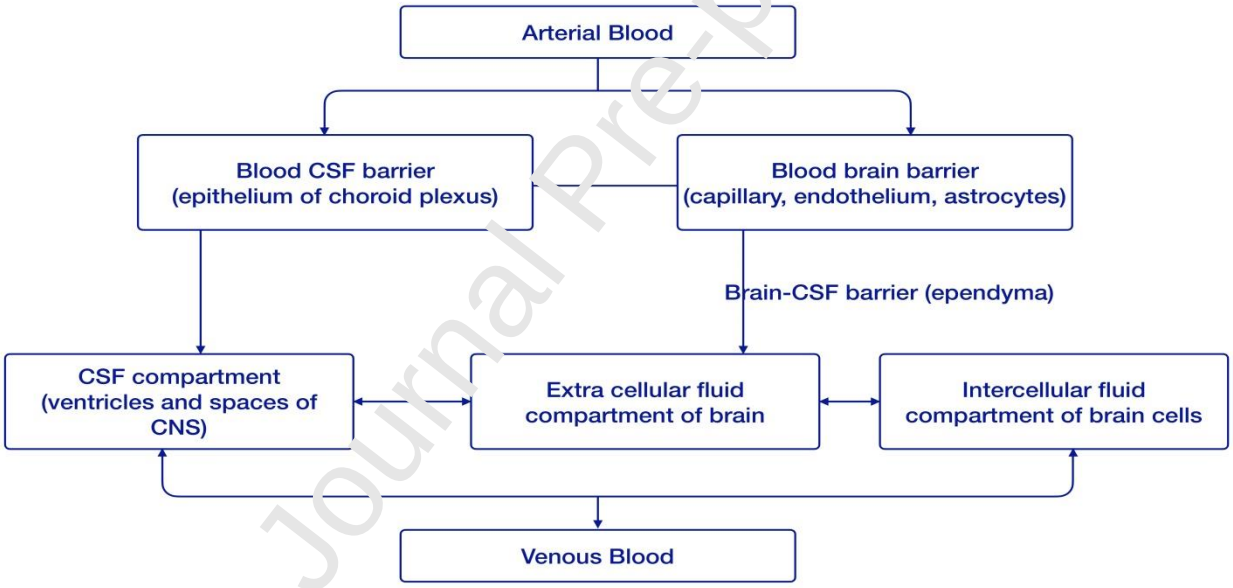

Fig. 4. Schematic presentation of BBB, CSF, Brain CSF [34].

3. Drug Delivery approaches to Brain

For effective drug delivery without any restriction, several drug delivery approaches have been investigated as shown in table1 [35]. Until now, these approaches include invasive, non-invasive, and miscellaneous techniques. These are described in Fig. 5. and details are given below [36].

Table 1. Approaches for drug delivery to the brain [35]

Approach	Advantages	Disadvantages
BBB disruption	Clinically applicable Enhanced stability of cargoes: non-immunologic	Nonselective; neurotoxic
Biotechnology based delivery	Effective route for the neuro-pharmaceuticals to the brain tumors and Parkinson's disease	grafts do not survive for long time
Chemistry based delivery	Re composition of the drug results in the generation of a prodrug	Adverse pharmacokinetics and the increased molecular weight of the drug
Intracerebral delivery	Sustained release. Favorable results are obtained with high level of drug concentration	Slow motion of compounds. Drug dosage restricted by implant size.
Intrathecal delivery	Cost effective with the least side effects	Highly invasive, poor patient consent
Intranasal delivery	Rapid absorption and onset of action; enhanced bioavailability	Decay of drugs via mucosal enzymes appropriate only for strong therapeutic drugs
Noninvasive delivery	Helpful in the passage of BBTB	widespread drug distribution Poor delivery of the drugs

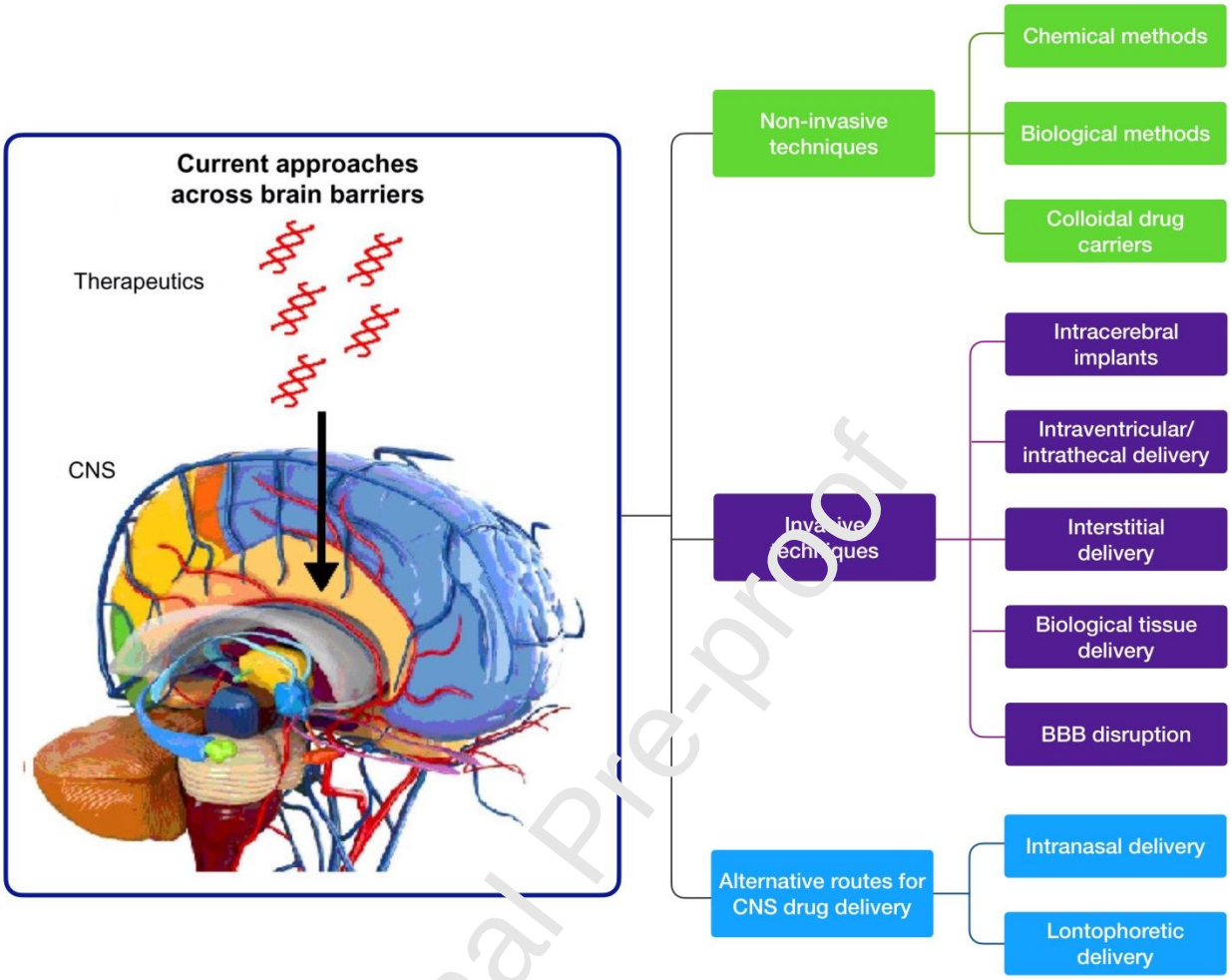

Fig. 5. Current approaches for brain drug delivery [36]. (Reproduced from an open access source.)

3.1 Invasive Approach

In the invasive method only lipid-soluble nutrients, a few peptides and low molecular weight molecules can pass through barrier to any significant extent either by using specific transport mechanisms or passive diffusion. Intracerebral and intrathecal administration is implied by direct invasive delivery of the drug into the brain and take a craniotomy. Both they can extensively deliver small and large molecules. Several compounds including includes toxic agents,

pathogens, and viruses etc., can be delivered into the CNS via this intranasal route The undesired release of anticancer agents to normal brain tissues, and physiological stress, are the main disadvantages caused by it [37-39].

3.2 Intracerebral delivery

To obtain more specific and successful release of drugs to certain parts of the brain, direct injection/implantation into the targeted part is introduced by stereotactic coordinates and /or continuous intraventricular infusion of the drug into the brain tissue. By using this method, favorable results were obtained in clinical trials of Parkinson's disease. The slow motion of compounds inside the brain due to the nearly arranged cells in both gray and white matter microenvironment was observed. Therefore, a higher dose for an appropriate drug concentration is required [40, 41].

The designed implanted devices are biodegradable and biocompatible based on polymeric matrix having encapsulated drugs inside. The skull is opened at the desired location of delivery where the reservoir is to be implanted. The penetration of the drug strongly depends on the physicochemical behavior of the drug, and normally limited amount of the molecule is delivered. e.g. an implant with nerve growth factor after placing inside the brain for the treatment of quadriplegic patients revealed better results[42, 43].

3.3 BBB disruption

In order to get more beneficial effects of drugs and their targeted release to the brain the membrane of the BBB is biochemically disrupted. Hence, this method involves direct administration of the drug substances to CNS by applying energy or certain chemicals. To specify the certain area of brain for target is the major advantage of this approach The

phenomena of BBB disruption occurs with the help of two approaches; Different chemical substances with higher osmotic pressure i.e. mannitol hyperosmotic solution is mostly applied to improve release of chemotherapeutic drugs to brain tumors [44]. This causes the endothelial cells to shrink and stretches the tight junctions whereas ultrasound and electromagnetic radiation causes shrinking of endothelial cells. The ultrasound waves with the recommended frequencies of 0.2-1.5 MHz are suitable for clinical applications. Thus intravenous injection of microbubbles are typically applied to reduced power requirements to disrupt the BBB that generally lasts few hours to < 1 day [40, 45-48].

3.5 Intrathecal delivery

Herein, the neurotherapeutic agents are directly administered into cisterna magna of brain through intrathecal route. This is the most suited route for drug delivery in the spinal diseases and disseminated meningeal diseases. To allow the delivery of a higher amount of enzymes to the brain is the main advantage of this method, thus the massive use of therapeutic drugs is not required. Moreover, this strategy controls the problems of short half-life of drugs into the blood, avoiding the problem of systemic exposure and toxicity. However, the risk of drug spread out along the distal space of spinal canal is the major disadvantage of this pathway [49, 50].

3.6 Noninvasive approach

Several non-invasive brain drug delivery methods enable brain blood vessel network to catch extensive drug distribution. This technique effectively helps drugs in passing the BBTB with the increase in BBTB permeability. The primary proteins in tight junctions (TJs) in the BBB are claudins, occludin and junctional adhesion molecules (JAMs). The expression of these TJ proteins could be decreased by microbubbles and ultrasound irradiation, which temporarily opens the BBB without any adverse effect on the normal brain tissue. These approaches are

usually dependent upon drug manipulations like receptor-mediated drug delivery, chemical drug delivery, prodrugs, lipophilic analogs, and carrier mediated drug delivery, etc. However, systemic delivery of the drugs to the brain in non-invasive approach has been a challenge resulting in the progress of new drug-targeting techniques [6, 37, 38].

3.7 Chemistry based approach

This approach considers the suitable chemicals for the delivery of drug substances via BBB. In this approach drug can be lapidated into two ways; firstly, the polar functional groups on the water-soluble drug can be concealed by conjugating them with lipid-soluble moieties. Secondly, the water-soluble drug can be conjugated to a lipid-soluble drug carrier. Although different ideologies have been developed for transporting the neurotherapeutics, these approaches have extensively been researched for the last two decades. Examples include chimeric peptides and cationic proteins [51, 52].

3.8 Biotechnology based approach

The scientists from the various other fields have shown considerable interest in the field of biotechnology. The ideas of this technique is to implant fetal neural grafts into the dysfunctional part of the brain and widely deployed in polymerase chain reaction protein engineering, and recombinant DNA. For the release of drug into the brain, the biotechnology provides an effective route for the neuro-pharmaceuticals to the brain and brain tumors too. This method is also very capable for the treatment of Parkinson's disease. Nevertheless these grafts do not survive for longer without neovascular innervation [36, 43].

3.9 Intranasal delivery

The intranasal route has been employed for direct drug release into the blood by passing the nasal mucosa for systemic action. This consumes the link of trigeminal nerves and trigeminal nerves in the nasal mucosa to the brain and requires small dose, self-administration, and avoids sterile techniques**.** This permits quick absorption and onset of action, an absence of hepatic, easy administration as well as bypassing gastrointestinal degradation and protein binding in the circulation. By that means drug bioavailability is improved and systemic side effects are reduced Examples of intranasal administration are the delivery of cytokines, neurotrophins neuropeptides genes, and chemotherapeutics. The obvious drawbacks of this approach include the decay of drugs by mucosal enzymes, administration not done by a medically trained professional, a short hold time in the nasal cavity, and restrictions determined by the nasal anatomy. Thus, these altogether follow short drug concentrations reaching the CNS [53-55].

4. Challenges for delivery to the brain for ND diseases.

In this section, we describe the challenges faced in the treatment of ND diseases and the applications of different therapeutic available options.

4.1 Alzheimer's disease

In the USA more than 5 million people have been affected by Alzheimer's disorder (AD) and this is the leading cause of global memory disorder, Accumulation of amyloid-beta peptide (Aβ) (senile plaques), memory loss brain atrophy presence of hyper phosphorylated tau filaments (neurofibrillary tangles), and cerebrovascular changes, as shown in Fig. 6, are the main characteristic of AD. Abnormal proteins, oxidative stress, reduced acetylcholine (ACh) levels and excessive metal ion accumulation in brain, and are so supposed to take part an important role in its pathogenesis. [56, 57]. AD is treated with two classes of drugs: cholinesterase inhibitors

and glutamate regulators. Cholinesterase inhibitors work by impeding the failure of the neurotransmitter acetylcholine. Vomiting, loss of appetite, nausea, and increased frequency of bowel movements are their side effects. The only approved glutamate regulating medication is Namenda this is used to treat Alzheimer's, which is connected to memory and learning. The effectiveness of Namenda is on par with the cholinesterase inhibitors, in that it works for approximately half of the individuals taking it, and then only for a short time. The side effects of Namenda includes headaches, constipation, confusion, and dizziness [57].

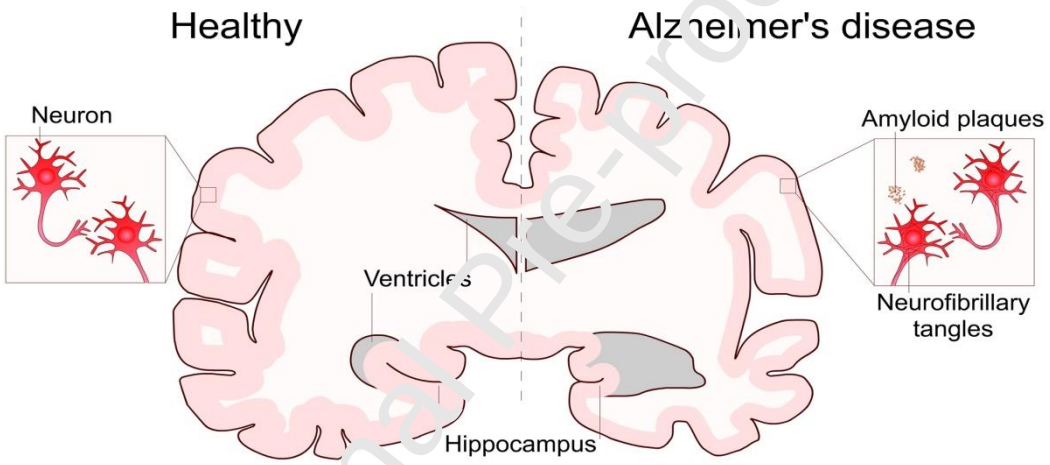

Fig. 6. Main pathologic hallmarks found in AD brain and nanoparticle [57]. (Reproduced from an open access source.)

Primary mental problems found in Alzheimer's disease (AD) brain and nanoparticle (NP) release systems used in pre-clinical animal models of AD. The main features of AD are the existence of amyloid plaques and neurobribrillary tangles in neurons, which results culminates in adverse neurodisorder.

4.2 Brain tumor

Most malignant brain tumors found in adults are of neuroepithelial origin and belong to the group of gliomas that depends on their similarity to glial support cells of the brain, oligodendrocytes and astrocytes. Malignant brain cancer is found and incurable diseases with high mortality rate. Drug delivery is seriously impaired by the structure of BBB in the diseased brain Different effective available drugs for brain tumors treatment are inadequate since poor delivery through the BBB is noted. The novel ways for the release of drugs include liposomes, micelles, and polymeric NPs (Fig. 7). But mainly these encapsulation approaches are expensive having less efficacy in encapsulation, and the systemic poisonous of the drugs [58, 59]. Cell encapsulation for prolonged delivery of the active therapeutic molecule, BBB circumvention is a promising technique for drug release [60, 61].

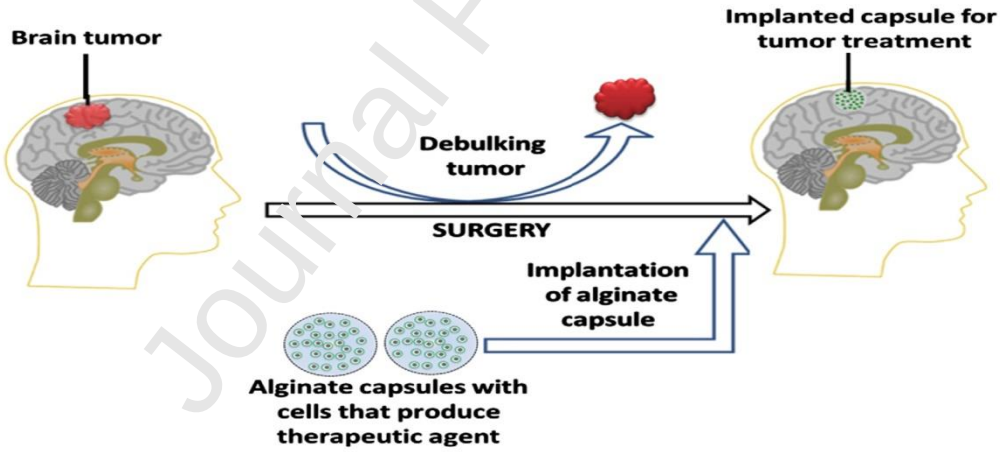

Fig. 7. Brain tumors treatment proposed by cell encapsulation, the therapeutic agent is produced by one or more implanted capsules with cells in the locality of excised tumor [61]. (Reproduced with permission.)

Suggested surgery for brain tumors with the help of cell encapsulation technique. At the time of surgery, the surgeon can implant one or more capsules in the immediate location of the excised tumor. Since the delivery of the therapeutic agent is local, undesired side effects from systemic incorporation are shut out. Significantly, the therapeutic are generated over prolonged periods and can kill the leftover of malignant cells.

4.3 Huntington's disease and Amyotrophic Lateral Sclerosis

These two ND ailments are of relatively less occurrence but are lethal and horrifying [62]. Huntington's disease (HD), the most common monogenic neurological disease present in developed countries, is an autosomal dominant disease that occurs on account of genetic mutation. The mutant form of Huntington named protein leads to that genetic mutation that ended up to neuronal death and dysfunction. The involuntary choreatic movements, dementia, and behavioral and psychiatric disorders are main characteristics of this ailment. The manifestation of HD starts in adult life progresses fast and unfortunately may takes the life of victim within years. Up till now no treatment is available for this disease, the single option is the management of the symptoms [63]. Tetrabenazine and Olanzapine are often prescribed drugs to treat HD but victims are in dire need of a permanent treatment of this terrific disorder.

Amyotrophic Lateral Sclerosis (ALS) or motor neuron disease is the one that is identified by the breakdown of lower and upper motor neurons that basically control actions of voluntary muscles. Muscle atrophy is the one main symptom of this disorder in which muscles decreased in size and lost their strength. Muscle stiffness, muscle twitching and cramps, difficulties in breathing, swallowing, eating, and speaking are some other associated problems. In severity full paralysis of voluntary muscles happened that may ended up with the death of victim [64]. On account of

its grave and lethal impacts many drugs have recently being experimentally analyzed for their utilization in ALS treatment like Masitinib, Ibudilast, Triumeq, Retigabine and Tamoxifen. However, only two drugs named riluzole and edaravone are currently available and being used. Unfortunately, even these two drugs are only effective to slow down the progression of the disease but cannot help to get rid of the disease fully and are unable to revert manifested symptoms of ALS [65].

4.4 Parkinson's disease

Parkinson's disease (PD) is caused by increasing lifespan and demographic changes in population and approximately 10 million people are affected by it throughout the world. The PD is distinguished by the selective breakdown of dopaminergic neurons in the substantia nigra (SN) and the existence of α-synuclein and protein inclusions termed Lewy bodies in neurons (Fig. 8). This disease may be treated with a multitude of medications; however, likewise Alzheimer's medications, they are normally effective only for a short period of time including Catechol O-methyltransferase (COMT) inhibitors, MAO-B inhibitors anticholinergics, L-Dopa, dopamine agonists and MAO-B inhibitors [57, 66].

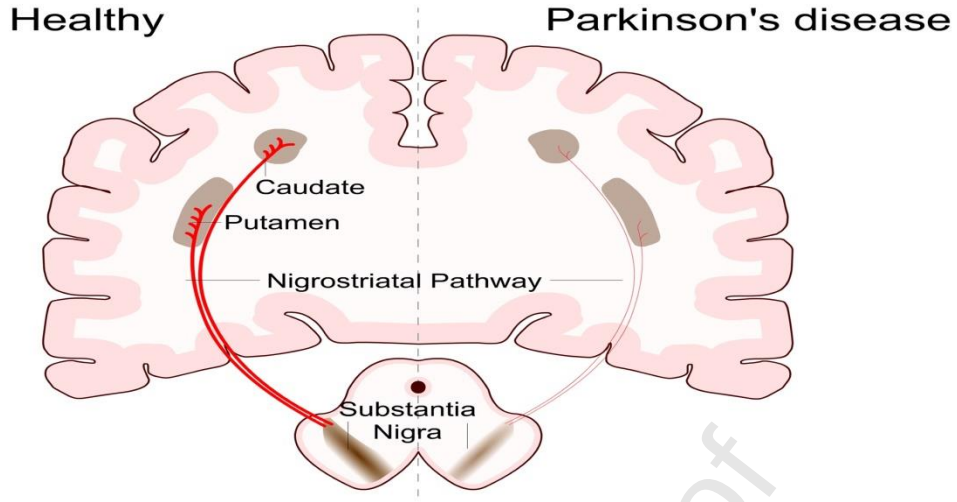

Fig. 8. PD hallmarks and used in pre-clinical animal trials of PD [57]. (Reproduced from an open access source.)

Parkinson's disease (PD) hallmarks and nanoparticle (NP) release systems applied in pre-clinical animal models of PD. The PD brain is identified by a specific loss of substantia nigra dopaminergic neurons, which lead to shrinkage of the cerebral and adverse neurodegeneration.

4.5 Stroke

The stroke is the long-lasting disabling and costly disease found in adults affected approximately 800,000 people per year in the world. This is caused by the blockage of vessels in the CNS. Experimental ischemia, conducted by growth of a penumbra and cell death, considers the main features of stroke in humans. Bleeding or occulation of vessel due to a blood clot throughout a stroke period prevents blood supply to brain (ischemic stroke) shown in Fig. 9, resulting in death of brain cell and eventually in patient death [67]. However, for the treatment of stroke, the only options available are rehabilitation programs based on patient's specific symptoms. For instance,

patients with strokes that have occurred in the area of the brain responsible for speech often show speech deficits treated by speech therapists. But some stroke patients can be diagnosed and treated in an emergency room within four hours of stroke onset, then some surgical options are also available depending on exactly how the stroke is happening, such as angioplasty to remove clots [57, 68].

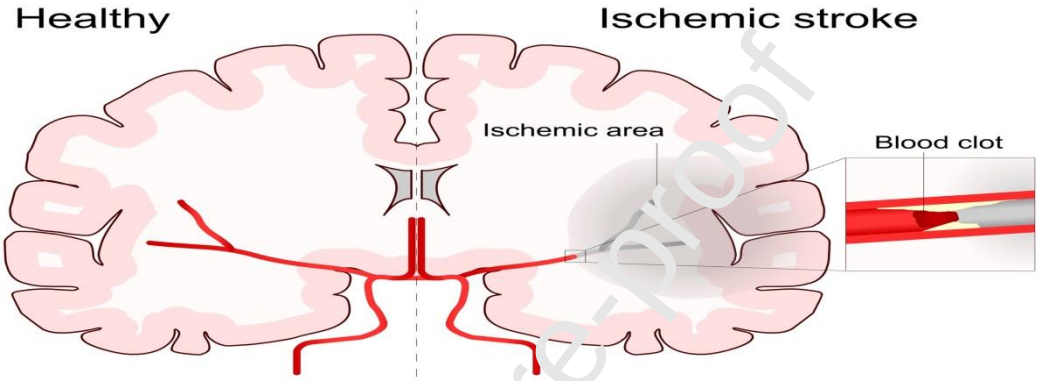

Fig. 9. Representation of the main cause of ischemic stroke which happens when blood flow is interrupted by nutrient depletion, clot culminating in oxygen, and resulting in neuro inflammation disorders [57]. (Reproduced from an open access source.)

Simplified description of the main event resulting in ischemic stroke and the most promising nanoparticle (NP)-based strategies applied in pre-clinical studies for ischemic stroke. Ischemic stroke happens when there is interruption of blood flow caused by a clot resulting in oxygen and nutrient depletion and hence in neurodisorder.

5. Novel approaches and biomaterials for the treatment of ND diseases

In this section, the details of latest approaches including tissue-engineering strategies, which are being applied for the treatment of ND diseases, are described.

5.1 Nanoparticles for brain drug delivery

NPs have gained significant importance in the release of drug molecules targeted to the brain from the last few decades. They have capability to pass the barriers and promote drug delivery. Nanospheres, nanosuspensions, nano-emulsions, nanogels, nano-micelles and nano-liposomes, polymeric NPs, carbon nanotubes, nanofibers and nanorobots, solid lipid NPs (SLN), nanostructured lipid carriers (NLC), and lipid drug conjugates (LDC) are employed as nano-systems in CNS disorders [56] [69]. Fig. 10 represents the most preferable types of NPs for the biomedical applications. NPs offer clinical advantages for drug release, for instance less drug dose, least side effects, and facilitate drug crossing across the BBB [70].

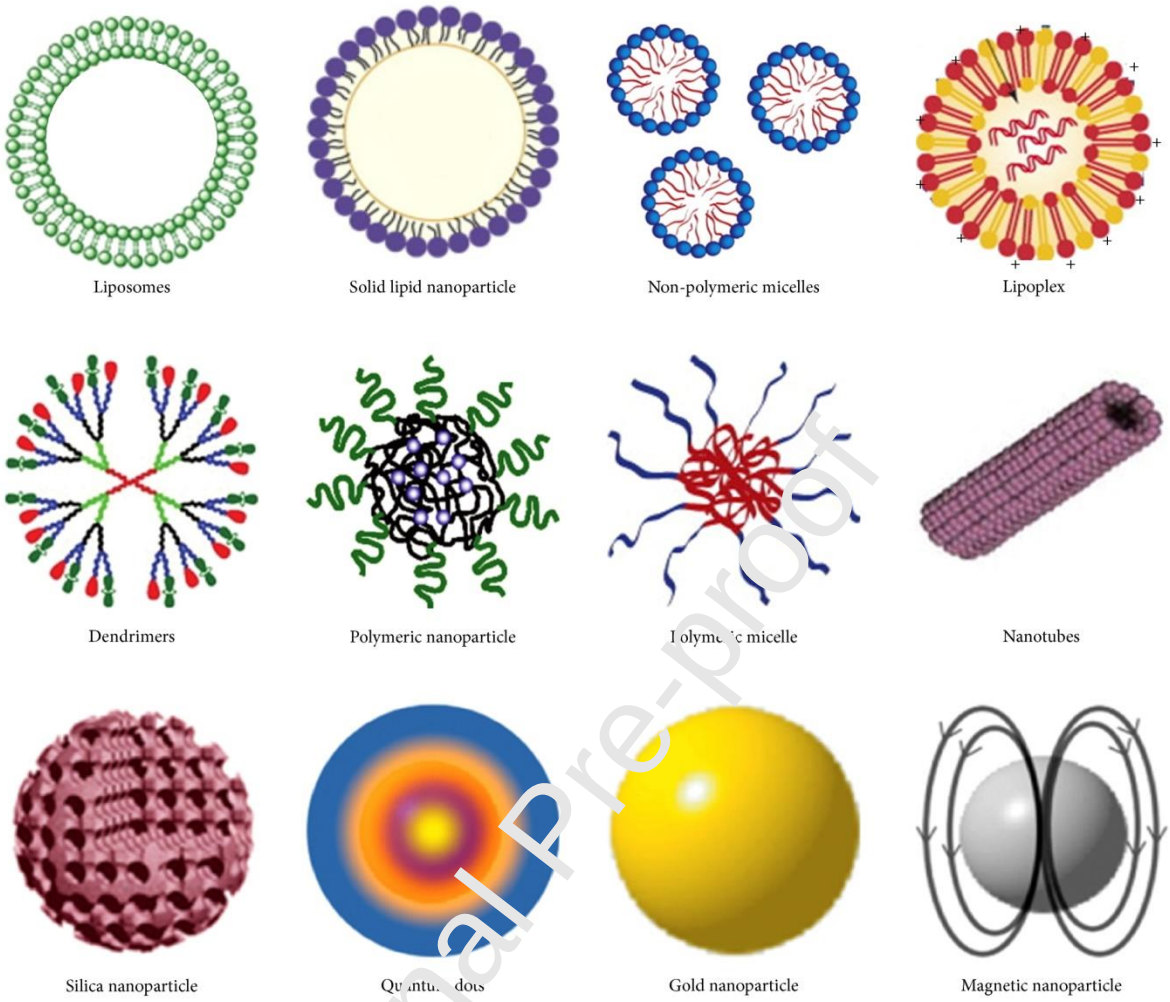

Fig. 10. Schematic representation of various types of NPs used commonly for biomedical applications [70]. (Republished from an open access source).

NPs are typically by a size not greater than 100 nm and have noteworthy potential for the release of drugs over the blood-brain barrier.

The optimized NPs are applied for passing through BBB by exploiting receptor-mediated and adsorptive-mediated transcytosis pathways in the systematic delivery of NPs (Fig. 11a). The locally delivered NPs fully bypass BBB and are depended upon convection enhanced delivery for the clinically relevant volume of distribution (Fig. 11b) [71]. Although, the enhancement of

brain drug delivery with drug-loaded NPs is very good, it is still quantitatively hampered than free drugs. In the context of brain disorder delivery of NPs through BBB is the first challenge. The principle tool in laboratory research and clinical surgery is imaging that has been used for the therapeutic effects of nano drugs for personalized medicine and examining pathologies at the initial stage. Liposomes, for example, display great potential to compartmentalize and solubilize hydrophilic and hydrophobic drugs shown in Fig. 12 [8, 72-74]. Further detailed research is necessary for the deep understanding of mechanisms maintaining this different NPs-mediated transport of the drugs to the brain [61, 62].

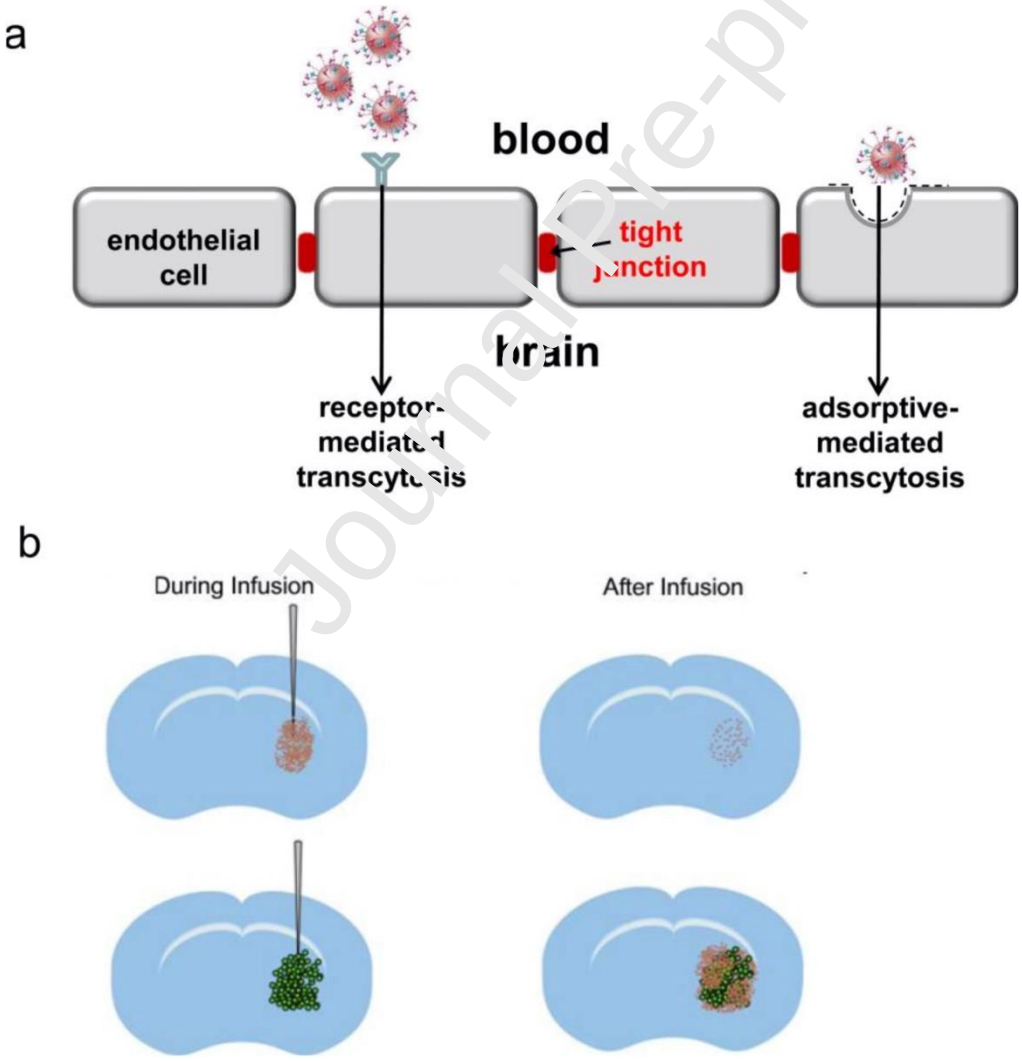

Fig. 11. (a) Systematic delivered NPs cross the BBB through either receptor-mediated transcytosis, , (b) NPs locally delivered bypass the BBB altogether and depend on CED to achieve enough distribution. With CED of free drugs (top row), there is enough initial distribution, but the drugs disappear quickly after the infusion stops.

[71]. (Reproduced with permission.**)**

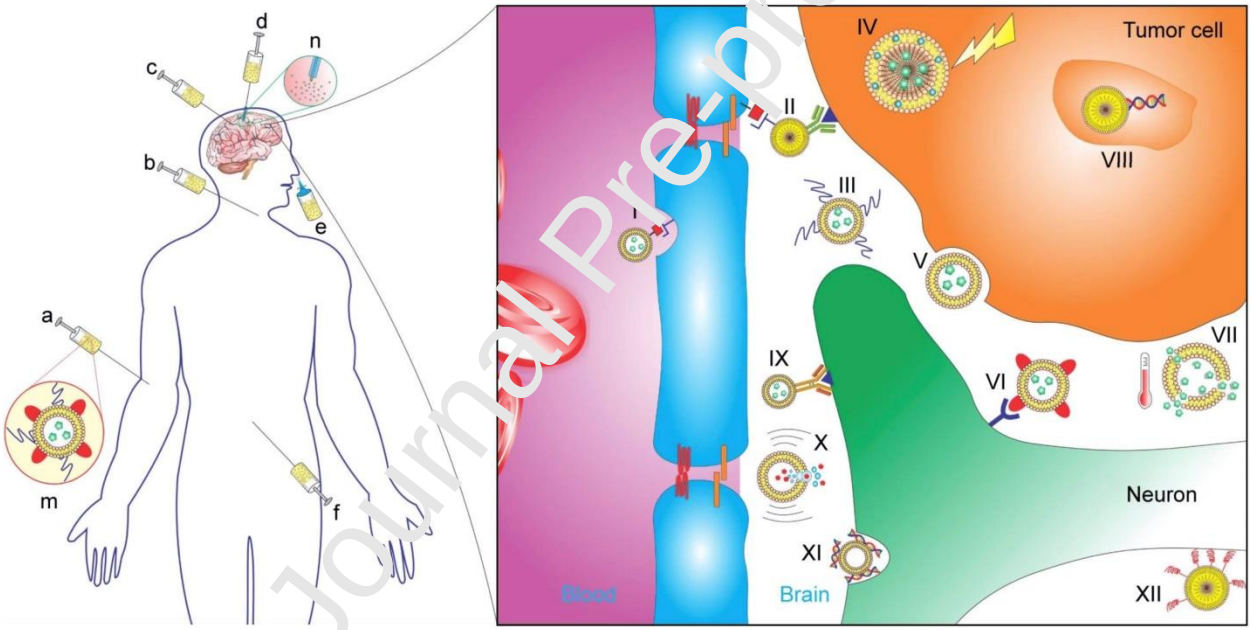

Fig 12. Liposomes release therapeutic molecules to CNS by (a) interacarotid, (b) interacranial, (c) ineranasal, (e) intraperitoneal, (f) interjection, (v) the ability to enhance blood circulation time is induced, (III) liposomes can pass BBB, (I) target the site of disease, (IX) or both, (II) surface modification of liposomes, (IX) RNA aptameter, (VI) or peptide, (XII) incorporation of cationic lipid, (VIII and XI) summary of therapeutic mechanisms, (IV) increased temperature, (VII) ultrasound [8]. (Republished from an open access source).

5.2 Neural tissue engineering

The central nervous system has been facing challenges in repairing the function of central nervous system due to its complications and restricted ability of regeneration [71]. Thereby providing new medical treatment alternatives to traditional transplantation methods is very important. With the advent of tissue engineering by using biomaterials novel strategies for neurological disorders can be considered. The result of CNS injury is activation of glial cell multiplying to generate an inhibitory glial scar. Currently, there is not clinically proven physiotherapy for actively obtaining better repair of the human CNS. Current treatments used in PNS damage are nerve autografts and allografts but the assessment of clinical results of autograft application showed that development of engineered alternatives is essential. Therefore, neurobiologists and neurologist surgeons face a challenge in restoring of damaged PNS and CNS, this may cause problems such as neuronal formation, infectious diseases, immunological issues and lake of donor nerves [75, 76].

5.2.1 Application of biomaterials in neural tissue engineering

The extracellular matrix performs numerous functions in the body such as structural and mechanical support to the tissues, holds the cells together facilitates migration of cells and communication within cells Polymeric biomaterials closely replicate the macromolecules that cells interact with in vivo. Successful nerve regeneration is obtained with the help of tissue engineered scaffolds having mechanical support of growing neuritis but remit biological signals to guide the axonal growth cone [77, 78]. Various biomaterials have been exploited for nervous tissue engineering, details are given below.

5.2.1.1 Natural polymeric materials for neural tissue engineering

Natural polymers being very much identical to the macromolecular substances have been applied in the nervous tissue engineering.

5.2.1.1.1 Collagen

Collagen being a suitable material for implantation is extensively studied for neural tissue engineering and only a few persons possessed humoral immunity against it. Rats, bovines and humans are the main sources of collagen. With the pH variation of collagen solution, gel formation is revived for the use as a potential scaffold. Scaffold quality may change at different concentrations of collagen. Recent studies have proven collagen as a suitable natural polymer for nerve tissue regeneration due to similar physical and mechanical properties to the normal nervous tissue [79]. At present collagen is the only clinically approved biopolymer in neural tissue engineering i.e NeuraGen® proved to be highly effective in peripheral nerve reconstruction. Another promising commercially available collagen nerve guide is Neuromaix® that also showed outstanding results in clinical practices [80].

5.2.1.1.2 Hyaluronic Acid (HA)

This is linear glycosaminoglycan having some sites for the adhesion of cells, and is an ideal candidate for CNS tissue regeneration due to the existence of HA in brain ECM. HA noticeably decreased glial scar formation after implantation which makes it an attractive option in fabrication of scaffolds for CNS regeneration. Combination of HA with ECM modification and release of antibodies (anti-NgRs) are highly biocompatible and hold great potential in neural tissue engineering [81].

5.2.1.1.3 Hyaluronic Acid Derivatives

The main drawback of HA is its poor adherence to the surface. Thus to promote its cell adhesion, the blend of HA with other materials are made. The blend of HA and collagen produced scaffolds with favorable mechanical properties for CNS regeneration. Hyularonane derivative produced by the esterification of hyaluronic acid with benzyl alcohol is the best choice for neural tissue engineering. This can be produced in the form of a variety of devices such as gauzes, nonwoven biocompatible fabric scaffold, tubes, and membranes [82, 83].

5.2.1.1.4 Chitin and Chitosan

Chitin and Chitosan are the most abundant polysaccharides present in the nature. The studies have proven that chitin and chitosan both are suitable for nerve cell adhesion, neurite outgrowth, biodegradable nerve guides and nerve cell adhesion. Their nano fibrous tubes transplanted into a rat sciatic nerve gap resulted in proliferation of neural stem cells (NSCS) [84] [85]. The combination of extruded chitosan agarose and alginate, resulted in a bioink seeded with front cortical human neural stem cells and after three weeks, signs of mature neurons were seen in immunohistochemical analysis [86].

5.2.1.2 Synthetic polymeric materials

Production of biocompatible, biodegradable, conductive and resistant synthetic scaffolds with a variety of mechanical features and degradation rate are very attractive for neurite outgrowth. They exactly mimic the biological and mechanical characteristics of ECM and cells in vivo and commonly applied for peripheral and central nerve injuries, both in vivo and in vitro. Details of some extensively used synthetic polymers for the fabrication of scaffolds are given below.

5.2.1.2.1 Poly L-Lactic Acid (PLLA)

PLLA is a biocompatible synthetic biomaterial used in various biomedical applications. It is regarded as an ideal cell environment for nerve tissue engineering. Nanostructured PLLA scaffolds have resemblance with natural extracellular matrixes such as high porosity and variable pore size distribution, high porosity and high surface to volume ratio. Studies have demonstrated that PLLA scaffolds efficiently promote neurite outgrowth and NSC differentiation. By that means they are suitable in neural tissue engineering applications [87, 88].

5.2.1.2.2 Poly-D, L- Lactic–co-Glycolic Acid (PLGA)

PLGA approved by FDA has been largely deployed as a biodegradable appropriate scaffold in biomedical applications and nerve tissue engineering. These are more hydrophilic and have shown promising results in wound dressings, bone repair and tissue engineering. But due to lack of cell adhesion many techniques such as blending, covalent attachment of adhesive peptides, hydrolysis and aminolysis, have been developed to modify cell adhesiveness and PLGA scaffold [89]. The hydrolyzed PLGA into glycolic acid and lactic acid is suitable for sustained drug delivery and brain-specific targeting via conjugation with various surface ligands [90].

5.2.1.3 Combination of poly glycolic acid (PGA) and poly lactic acid (PLA)

The poly lactic co-glycolic acid copolymer is the formulation of PLA and PGA. Hydrolysis of ester bonds if happen after implantation leads to degradation into by products. These byproducts can reduce pH around implantation location after absorption by host tissue. PLA degrades at slower rate due to less crystalline in nature. PLGA is mostly applied as a polymer scaffold in tissue engineering, as a material for DDS, orthopedic appliances, sutures, and other biomedical applications. The galantamine loaded poly(lactic-co-glycolic acid) (PLGA) NPs showed high

encapsulation efficiency and sustained drug release, maintaining galantamine pharmacological activity for intravenous delivery using nano-emulsion in AD [91, 92]

5.3 Drug delivery through implants

Despite substantial development in microsurgical techniques, patients with peripheral nerve injuries hardly get full recovery. An alternate option is applying of acellular nerve allografts (ANAs) and processed nerve allografts [49]. ANAs provide a biological substrate for nerve regeneration without the requirement of immune suppression [93].

5.3.1 Tissue engineering/drug delivery through implanted scaffolds

Polymer scaffolds of implanted design are the pre fabricated forms of two or three dimensions with the potential of repairing tissues. This class of implanted polymers include thin films polymer membranes, conventional and printed 3D devices as shown in Fig. 13 [94].Their combination with regenerative approaches result in treatment options for neurodegenerative disorders. The regenerative medicine approaches are critically required to overcome disease progression and facilitate tissue regeneration [74, 95].

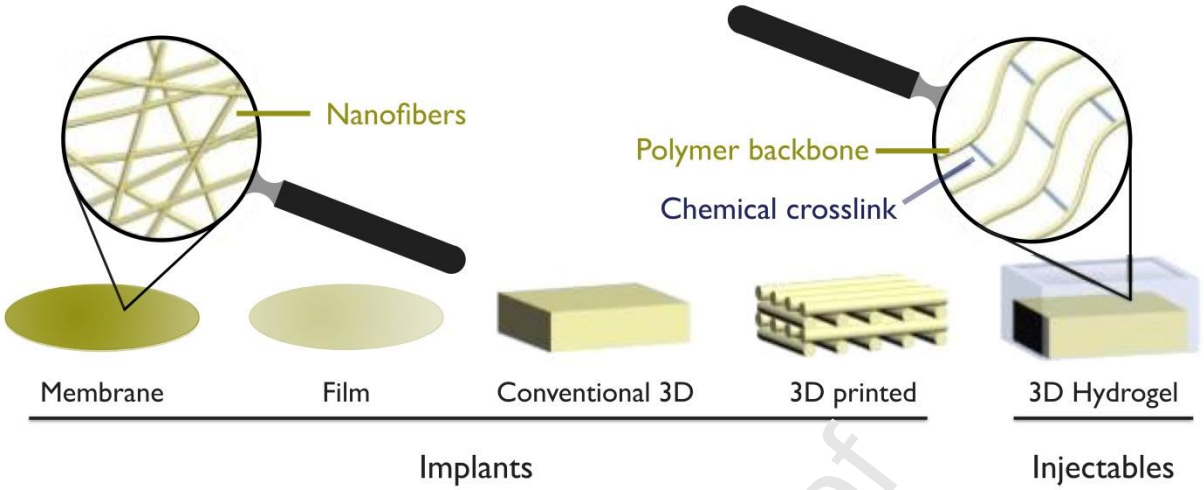

Fig.13. Illustration of different classes of polymer scaffolds [94]. (Reproduced with permission.**)**

Cell distribution, cell survival/viability, and host tissue integration are the major challenges faced to release the promise of cell transplantation in regenerative medicine. Therefore, some implanted polymer scaffolds and injectable hydrogels by incorporating specific chemical have been developed to mimic the cell's ECM. Hyaluronan with anti-inflammatory properties is a naturally found polysaccharide present in the ECM of the central nervous system. This can interrelate with various HA-receptors (such as hyaluronan-mediated motility receptor and CD44) found in various cells to raise cell adhesion and survival used [95]. The cell therapies and biomaterial scaffolds both together have made possible the physical support for transplanted cell engraftment and separate the implanted cell from the host tissue as explained in Fig 14 [96]. PEG-PLA NPs are used for the release of neuroprotective peptide NAP (NAPVSIPQ) into the brain through tail-vein. The transport of NAP is promoted with the help of transferrin-mimetic

peptide (B6: CGHKAKGPRK). Their tail-vein injections resulted in greater accumulation of the B6-PEG-PLA and lactoferrin-PEG-PLA NPs in the brain [95].

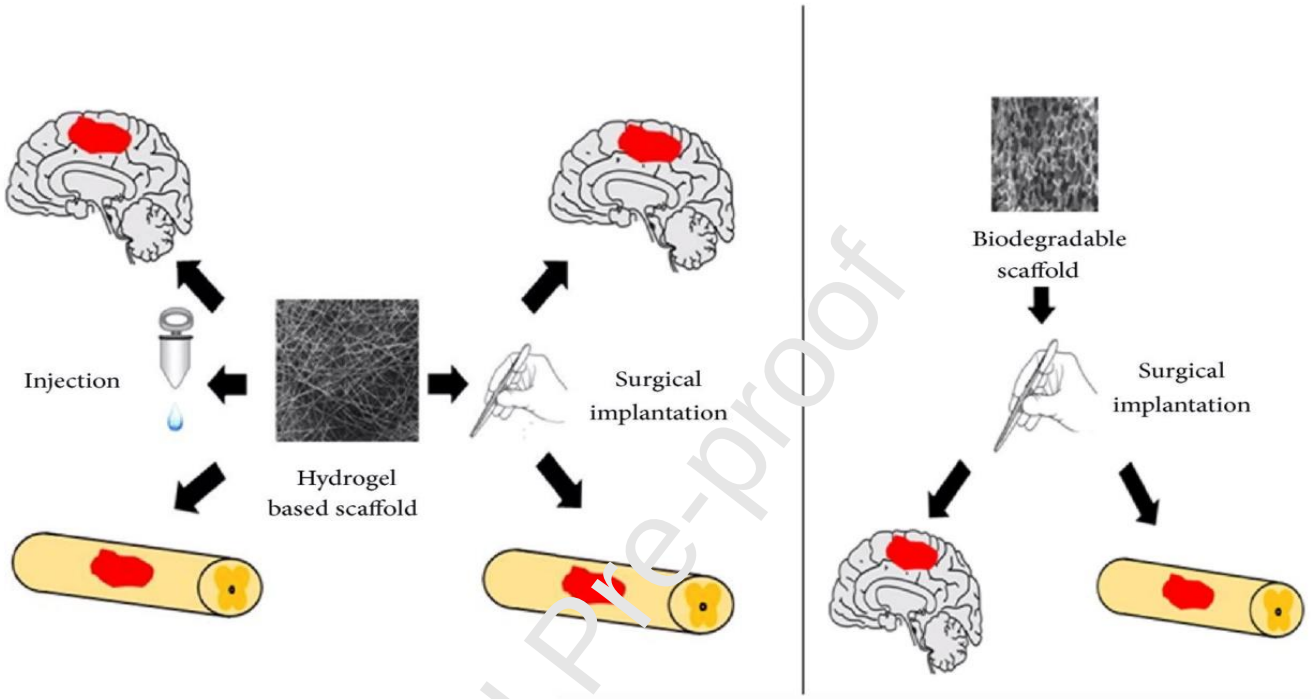

Fig. 14. Uses of biomaterials in regeneration of brain [96]. (Republished from an open access source.) :

Application of biomaterial scaffolds in regeneration of central nervous system

5.3.2 Tissue engineering/drug delivery through injectable hydrogels

Injectable hydrogels resemble to the native CNS tissue in mechanical properties and offer a minimally invasive approach for drug release. Thereby they are the most investigated materials for regeneration in local drug delivery to the CNS. The biocompatible, biodegradable and injectable hydrogels composed of hyaluronan (HA) and methycellulose (MC) own rapid

gelation, and ability to maintain cell viability. Hence showed high potential as a scaffold for cell transplantation therapy [97].

5.3.2.1 Insulin-like growth factor-I (IGF-I)

Insulin-like growth factor-I (IGF-I) named as somatomedin C and sulfation factor is a pleiotropic protein that possesses the ability to act i n various tissues and organs. It is categorized as one of the principal trophic factors present in circulation, and its role in peripheral tissues is well studied. [98]. IGF-I growth factor has role in sustaining integrity and homeostasis of brain and central nervous system. The presence of IGF-I receptors inside nervous system with addition of its neuroprotective effects on different types of brain cells make it a suitable candidate to treat ND disorders such as AD, ALS, PD, diverse neuropathies, and brain trauma. It also has tendency to block both necrotic and apoptotic cells death, by activating PI-3/Akt kinases pathways [99]. Tumor promoting capacity of this growth factor could be minimized by utilization low doses for longer duration of time [100].

6. Neural drug discovery: A new promising approach

The drug development for ND diseases is a high-risk therapeutic area where only 12% of all the drug candidates that are subjected to clinical trials, got approval for human use. Most of these approved drugs (12%) can only decrease the disease symptoms to some extent but are not successful to prevent disease progression [101]. In the United States adverse drug reactions becoming the fourth leading cause of death which indicates that current drug testing practices are not sufficient to predict drug toxicity in clinical trials [102]. The pharmaceutical industries require improved model systems to better understand the complicated pathways involved in progression of different ND diseases and for predicting possible drug toxicity reactions to

decrease drug related adverse effects [103]. In this context, in vitro human disease model systems are interesting candidate to understand human disease pathology in a better way and to push boundaries for the development of patient specific drugs.

6.1 Induced Pluripotent Stem Cells (iPSCs) as a novel tool in drug discovery and development for neurodegenerative diseases

The IPSCs are generated from skin or blood cells, and have been reprogrammed back into an embryonic state and can be used for the development of any type of human cells required for therapeutic purposes [104]. IPSCs generation and their conversion into stable neural stem cell lines (NSC) with a wide developmental capacity have created tremendous interest in the context of creating disease-relevant in vitro human models for phenotypic and target based drug screening and disease and patient specific drug discovery [105].

Animal disease models have been used for a long time in the drug discovery and preclinical studies. In addition, to assess efficacy of drugs before clinical trials, animal disease models are also valuable tools to find the etiologies characterized by human diseases and their specific targets for drug discovery. Although, various transgenic animal models have been generated but no one has recapitulated the full spectrum of human disease pathology. Because, while using animal based disease models their existed species differences, which in most of the cases leads to misrepresentation of human diseases, especially in case of small animals when they were used in neuronal disease modeling [106, 107]. Moreover, in most cases the positive efficacy results obtained from animal disease models were unable to reproduce in humans [108]. There are some other limitations which are associated with the use of large animal models such as longer experimental period, higher cost, and ethical issues [109]. In this way, human IPSCs technology

has opened new doors for disease modeling and patient specific drug discovery. In the development of human disease model, patient-derived IPSCs and cells derived from them are considered more relevant candidates for neurological diseases studies [110, 111]. For IPSCs disease model preparation, as shown in Fig. 15, IPSCs can be obtained from somatic cell samples of patient, such as peripheral blood, keratinocytes, dermal fibroblast, urine and hair follicles of patients [106].

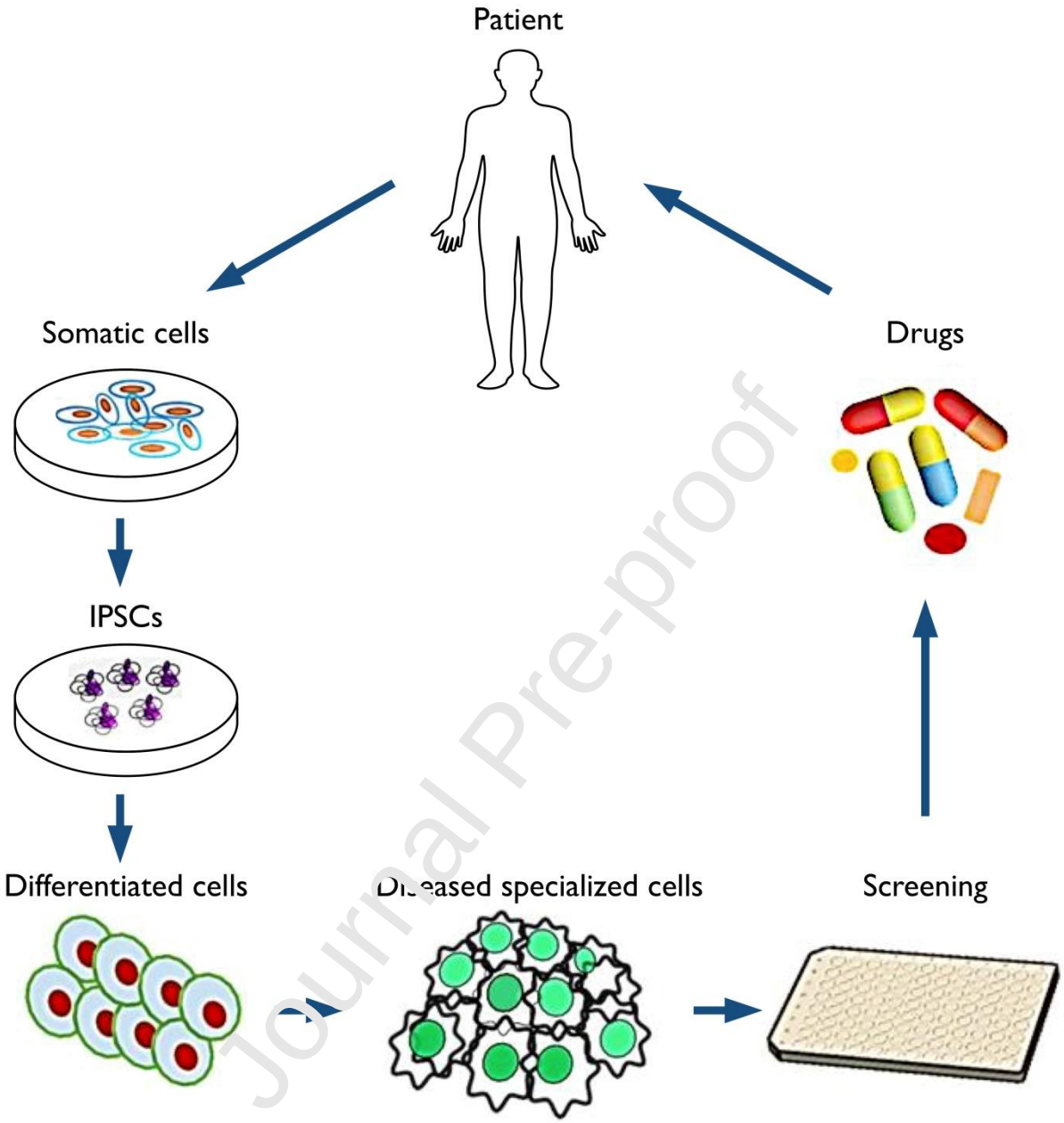

Fig.15. Schematic representation of IPSCs approach in drug discovery and development, leading to new therapies for neural diseases.

IPSCs cell lines can be generated using various gene delivery methods (non-viral reprogramming method, reprogramming by non-integrating viruses, mini circle vectors and single cassette

reprogramming vectors.) They can proliferate easily and are capable to differentiate into many cell types, such as (NSCs) (neuronal progenitor cells (NPSCs), different types of neurons, (such as motor & sensory, glutamatergic, serotonergic, cortical and dopaminergic etc) and 3D neuronal cell culture systems (in the form of mini brain organoids for neurological studies in more complex and coordinated environment). These IPSCs generated specific neuronal stem cells, different types of neurons and mini brains are used in assay development, drug screening, drug molecule development and finally new drugs after clinical trials are subjected to patients with ND diseases [104].

Although, IPSCs have been used for cell transplantation, to treat different neurological diseases still there are certain limitations which are associated with their use as a disease modeling system. These limitations include genetic and epigenetic variations that may occur in IPSCs due to prolong culturing [112]. Secondly, the environmental factors that play a key role in development and progression of neuropsychiatric diseases such as anxiety and depression, are missing in case of in vitro disease modeling [113]. Despite of these limitations associated with IPSCs disease modeling, it is still an important and good alternative to animal disease models for disease and patient specific drug discovery [105].

The IPSCs technologies are continuously developing and researchers are trying to overcome the shortcomings associated with IPSCs derived disease models as a representation of human neuronal diseases. A thorough understanding of these complex diseases at molecular level using *in vitro* disease model and followed by the accurate and effective drug development would help in finding solution of various challenges currently present in treating ND diseases.

7. Future direction and conclusion

ND diseases are the most devastating challenge all over the world, and in the future increased number of ND patients are expected due to worsening of the life style and burden. Even though developed strategies effectively offer delivery of drugs into the brain of these patients. But none of these approaches provide satisfactory results in the cases of CNS diseases disorder. This remains a challenge due to the unique physiology of the brain, including tight regulation and limited distribution of substances along ECF flow routes. Thus, immediate development of novel approaches for ND diseases are highly demanded that can impede the disease progression. Nanoparticles (NPs) are regarded as an ideal drug delivery system into inaccessible organ like brain, which blocks therapeutic agents delivery. The use of nanotechnology in drug delivery has opened various opportunities for the scientists to develop better therapeutic agents delivery devices for CNS. An attractive challenge will be the use of NBDDS for integrated therapy and diagnosis strategies (theragnostic) Therefore Innovative delivery systems should be look forwarded to promote brain disease diagnostics. In this regard, tissue engineering could be promising option for the replacement of fractions of tissues, or the whole tissue and have fulfilled the need for new organs and tissues replacement. TE involving the use of “hydrogels” especially injectable hydrogels as a scaffold material that structurally resemble the extracellular matrix of the human body, for local and controlled drug facilitate neural regeneration. Examples of such 3D gels are collagen and fibrin and sheets of cells being used with varying degrees of success with the advantage of releasing growth factors. The co-delivery of cells and biomolecules has revealed improved cell survival, cell function, and tissue regeneration. Until

now, key mechanisms underlying the success of co-delivery remain unclear, and the challenges of large-scale cell production and cell fate must be investigated for clinical use.

8. Conflict of interest

The authors declare there is no conflict of interest.

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