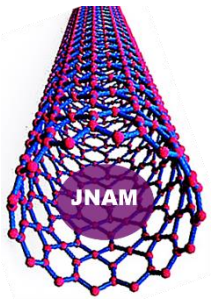
Journal of Nanotechnology & Advanced Materials
An International Journal

http://dx.doi.org/10.18576/jnam/080103



Nano Drug Delivery Systems Targeting Microglia for the Treatment of Brain Disorders

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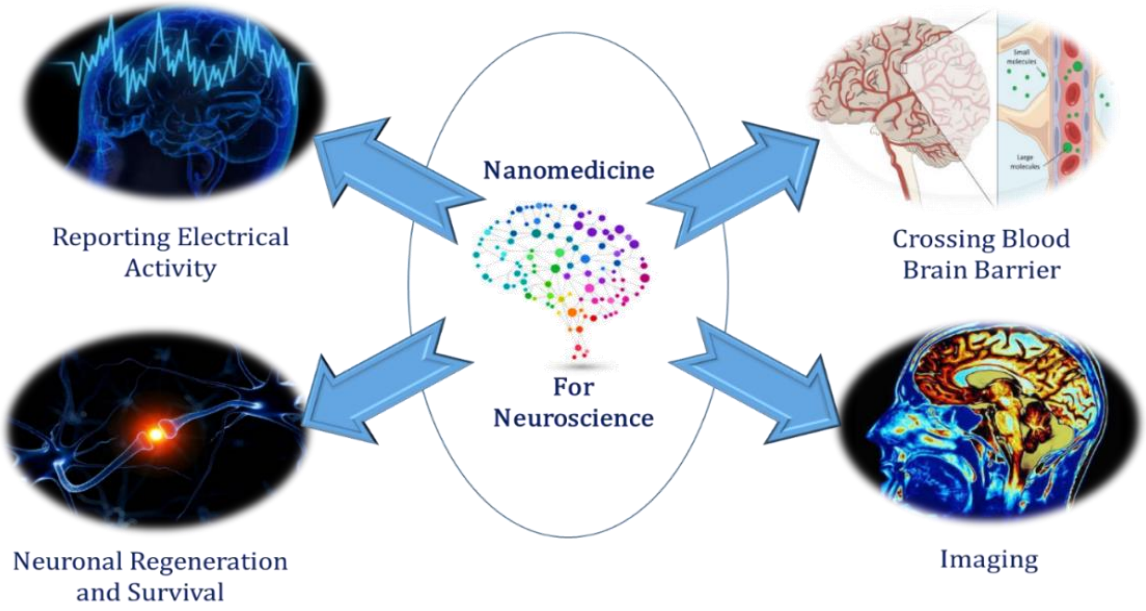
Received: 1 Nov. 2019, Revised: 21 Dec. 2019, Accepted: 27 Dec. 2019.
Published online: 1 Jan 2020.

Abstract: Nanomedicine is a field where the progression of nanotechnology is recruited to serve health and medicine. It has opened new avenues to understand and tackle many sorts of interactions between the living tissues, which were undoable with macroscopic materials. Nanomedicine took neuroscience to a next era, where targeting many neurological and psychological diseases became no longer a challenging task. Many recent types of nanoparticles became able to cross the blood brain barrier and targeting specific brain areas. Brain disorders including Alzheimer, Parkinson, schizophrenia and others were found to be strongly connected to neuroinflammation, and accordingly to immune cells of the central nervous system, microglia that play a key role in neuroinflammation. However, their mechanisms of action are not fully understood, and hence, recent studies are competing to solve this mystery using nanoparticles as a helping hand. In this review, we summarized the use of nano drug delivery systems to target microglia in different neurodevelopmental and psychological disorders aiming that research could take a step further towards achieving improved brain targeted drug delivery.

Keywords: Nanoparticles, Drug delivery system, Targeting Microglia, Brain Disorders.

Graphical Abstract



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1 Introduction

Nanotechnology is a reticulated field of science dealing with manipulation of matter on an atomic, molecular, and supramolecular scale. As an interdisciplinary field, the peculiar areas of nanotechnology overlap to melt the boundaries between the various natural sciences [1]. Nanomedicine is a field where the progression of nanotechnology is recruited to serve health and medicine. Hence, success of nanomedicine depends particularly on the significant advances being made in nanotechnology. [2]

It is noteworthy that the extremely small size of nanoparticles and the other materials on the nano-scale is important to understand when addressing nanomedicine, as it allows many sorts of interactions or contacts between them and the living tissues, which are undoable with larger materials [3]. The diameter of a typical nanoparticle of medical usage is in the range of 10 to 100 nanometers (nm) which is much smaller than that of a cell but corresponds to the size of most viruses [4].

Nanomedicine is a comparatively young branch of science that started in the 1990's when nanotechnology was first used in pharmacology, medicine and medical technology [5]. Nanotechnology itself has evolved few decades ago, specifically, at the beginning of the 20th century after the door to nano-cosmos burst open with the invention of the high-resolution electron and scanning tunneling microscopy. Once evolved it was rapidly integrated in biology, physics and chemistry [3].

Despite being used in a wide variety of applications in medicine, nanotechnology's key role in medicine is the development of nanoparticles-based therapeutics. Nano-formulated drugs are characterized by having several physical advantages which may be lacking in the drug alone [6]. These advantages include for instance, the increased stability rate/decreased physiologic clearance rates, reduced toxicity, improved solubility as well as enhanced clinical efficacy [7]. These characteristics are not limited to specific particles but rather can be controlled and modified for allowing the accurate evolving of drug delivery vehicles with the most plausive physical properties [8]. In addition, and owing to the fast elaboration of nanomaterials sciences, drug targeting can be reinforced by either adding specific molecular tags or by semi-selective properties inherent to nanomedicines [9].

2 Nanomedicine and Neurobiology

Owing to the mysterious brain and its many unrevealed mechanisms of actions, the treatment of neurological and neurodegenerative diseases remains a great challenge. These pathological diseases such as Huntington's disease, multiple sclerosis, Parkinson's disease, brain tumors, Alzheimer's disease, depression and autism are among the most untreatable syndromes [10, 11].

Up to now, very limited improvements come forth from clinical treatments of central nervous system (CNS) diseases, and the reason is that about 98% of pharmacologically active drugs against brain pathologies don't have the ability to reach the brain and exert its pharmacological activity because of the blood brain barrier (BBB) [12]. BBB is the primary interface of the brain, where it creates a very high density capillary network which supply almost every neuron with an individual blood supply [13]. This complex interface consists of endothelial cells, which are connected to tight junctions, hence preventing the diffusion of large hydrophilic molecules and microorganisms as bacteria to the brain extracellular fluid [14]. Successful passage of certain compounds through the BBB depends on their diameter, surface charge and lipo-solubility [15]. Out of this point, researchers shed more light on using nanocarriers to target brain diseases [16] (Fig. 1).

The use of nano-vehicles to deliver therapeutic agents to the CNS represents a promising strategy through the recruitment of well-designed biodegradable polymeric nanoparticles [17]. This recent approach has depicted two main advantages; firstly, the ability to modify the nanoparticles' surface in such a way that enables them to enter the brain via receptor-mediated pathways after intravenous administration [18], and secondly, this approach doesn't require any modification of the drug molecules for the brain delivery. Instead, the unfavorable physiochemical characteristics of the drug molecules are greatly improved upon their incorporation into appropriate nanocarriers [19].

3 Types of Nanoparticles Specifically Targeting Brain and Cross the BBB

Many types of nanoparticles have been developed recently to deliver various CNS drugs to the brain. Depending on the fabrication and uploading methodology, various drug carriers in the size of (1-1000) nanometer range have been developed in the form of liposomes, micelles, nanogels, nanoemulsions, quantum dots, dendrimers, exosomes and polymersomes [20,21] (Fig. 2).

3.1 Lipid-Based Nanoparticles

Lipid-based nanoparticles could be one of two main subtypes.

A. Liposomes

Liposomes, the first generation of nanoparticles, are small artificially synthetized vesicles that were first developed in 1965 as gene and drug delivery carriers [22]. They are spherical shaped vesicles made from natural nontoxic phospholipids and cholesterol. Being constituted from one or more vesicular bilayers (lamellae), liposomes have the ability to trap both hydrophilic and hydrophobic compounds avoiding the decay of the snared combinations

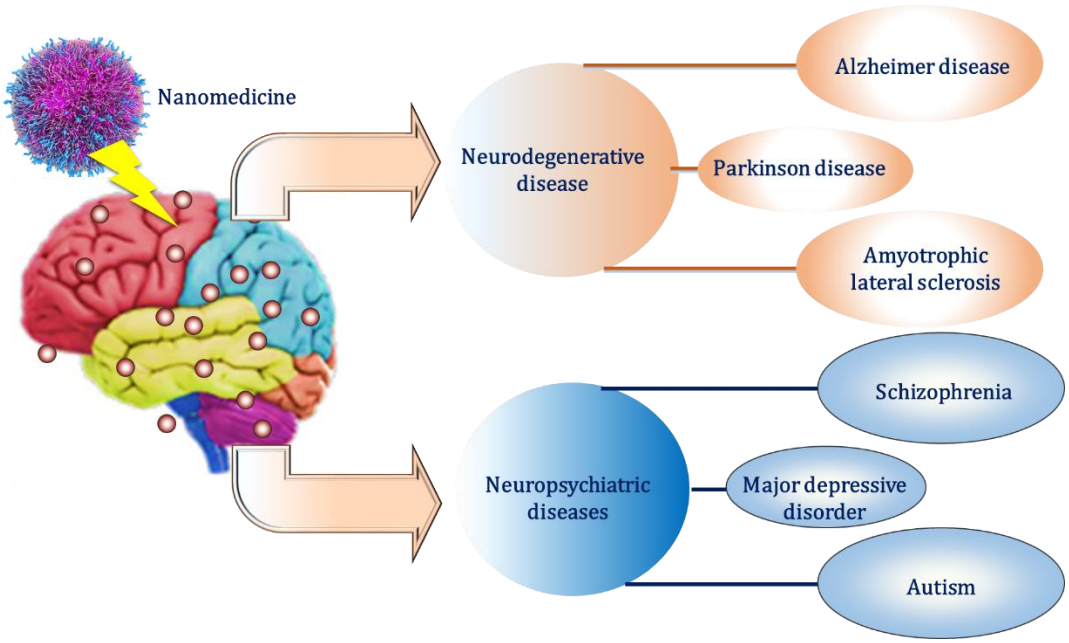

Fig.1: A schematic illustration of the pivotal role of nanoparticles as drug carriers for efficient treatment of psychiatric and neurodegenerative diseases.

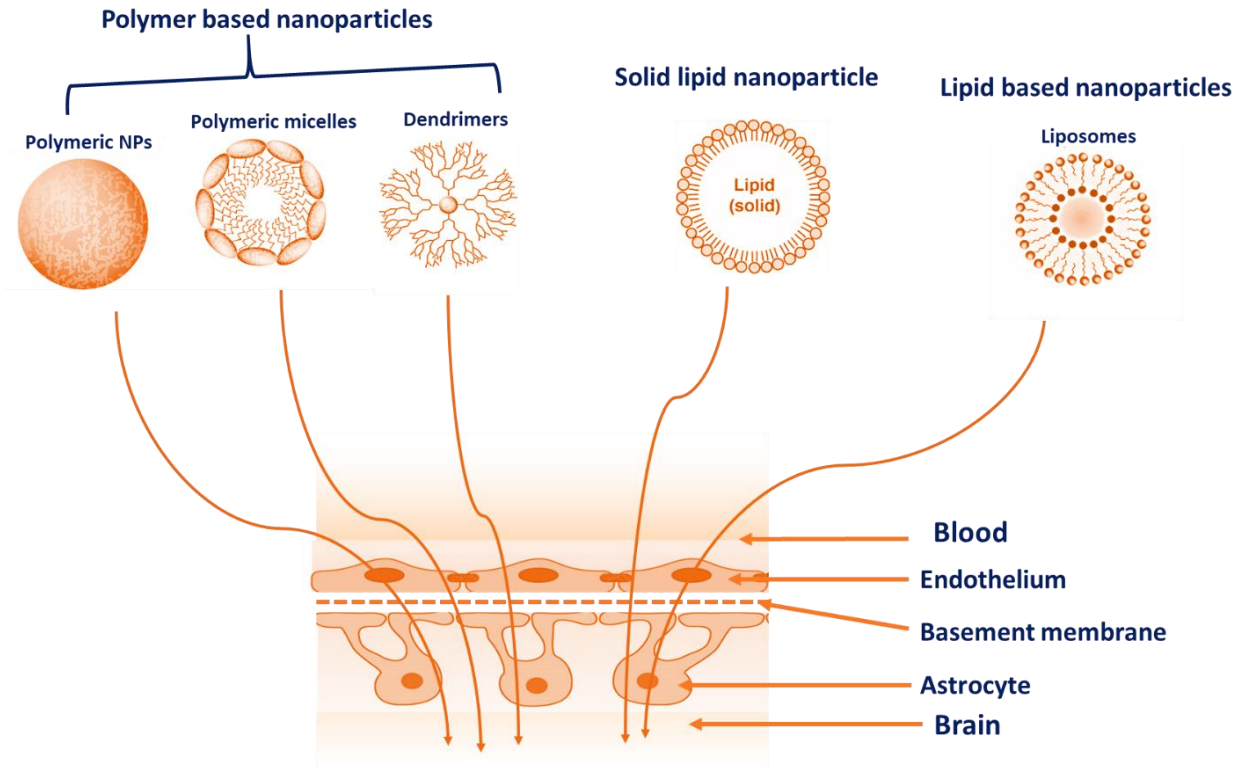

Fig.2: Various types of nanoparticles that cross the blood brain barrier.

as well as releasing the entrapped cargo at intentional targets [23]. Based on their biodegradability, low toxicity and biocompatibility, many liposomes-based clinical formulations are approved commercially [24].

Ibrahim *et al.,* designed Ser-HCl-loaded pegylated and glycosylated liposomes having the ability to cross BBB. Herein, this proposed vector showed promising results in crossing BBB by GLUT1 that could be significantly inhibited by cytochalasin B and phenobarbital. Furthermore, using C6 glioma cell line model, time-lapse live cell imaging and flow cytometry, it was found that glycosylated liposomes can pass the BBB by transcytosis and endocytosis [25]. In addition to that, Kairong *et al.,* showed that paclitaxel-loaded liposomes conjugated with TR peptide (PTX-TR-Lip) have potential ability to across the BBB and delivering therapeutics to glioma cells. Also, it showed potency in killing cancer stem cells and destruction vasculogenic mimicry (VM) channels [26]. Moreover, Jian *et al.,* have designed doxorubicin (DOX)-loaded liposomes conjugated with folate (F) and transferrin (Tf) for effective targeting glioma. Herein, there is observed ability for crossing BBB, increased survival rates and decreased tumor volume [27].

B. Cationic Liposomes

Cationic liposomes are positively charged lipids which are used to transfer the genetic materials as DNA into the cells and can't be degraded by lysosomes, therefore known as transfection vehicles [28]. Bolaamphiphiles is an example of cationic liposomes, which are characterized by having a strong shield surrounding the incorporated drug as this shield is composed of hydrophilic groups surrounded by a hydrophobic chain [24].

Bruce *et al.,* have described the potency of cationic liposomes to incorporate siRNA and acetylcholine acting as a molecular messenger for delivery to neurons. Further, this delivery system protects the cargo from serum degradation. Herein, there is observed significance in crossing the BBB and potential ability to treat prion and other neuropathological diseases [29]. Moreover, Mattia *et al.,* have designed a cationic liposome to include model protein (ovalbumin) with concentration 50 mg. This study confirms the importance of this non-invasive delivery system to cross the BBB for treatment of CNS disorders [30].

3.2 Solid Lipid Nanoparticles (SLNs)

As an alternative for polymeric carriers, solid lipid nanoparticles (SLN) were developed for the first time in the early nineties. SLN are considered the most efficient lipid-based colloidal carriers because they are stable with solid lipid core (hydrophobic) with the drug can be either dissolved or dispersed [31]. Triglycerides, waxes or fatty acids in the size of submicron, ranging from 50 to 1000 nm, constitute the SLN making them physiologically adequate lipid components that are solid at room temperature. Besides, the small size of SLN allows them to escape the reticuloendothelial system of the BBB. In addition, SLNs are characterized by being physically stable [24,31].

Shi *et al.,* have encapsulated camptothecin (CA) in SLN, and this study showed promising and effective targeting of the brain through efficient crossing of BBB. Furthermore, there was an observed decrease in the systemic toxicity and reduction of drug dosage [32]. Moreover, Yashwant *et al.,* have optimized transferrin-conjugated SLNs incorporating quinine dihydrochloride for brain delivery. This drug delivery system depicted the potential to transport the therapeutic molecules to cross BBB. Besides, this study showed that this system could be used in treatment of many neurological diseases such as Parkinson's disease, Alzheimer's disease, brain tumors and meningitis [33]. Furthermore, Montenegro *et al.,* have fabricated and assessed the SLNs as a carrier for the antioxidant agent, idebenone. They tested this drug delivery system across MDCKII-MDR1 cell monolayer as an *in-vitro* model of the BBB. Herein, it is not worthy that, idebenone permeates via transcellular pathway indicating that this strategy is promising for idebenone administration to the brain [34].

3.3 Polymer-Based Nanoparticles

A. Polymeric Nanoparticles

As revealed by the name, polymeric nanoparticles are made from polymers at the nanoscale of (1-1000) nm, and this category of nanoparticles found to be one of the most promising drug delivery systems to the brain in the last decade. Polymeric nanoparticles are synthetized in a way that the drug can be either loaded into a solid or liquid state. The drug can also be adsorbed or chemically linked on the nanoparticles surface [35]. Moreover, polymeric nanoparticles demonstrated a good ability to increases the stability of volatile pharmaceutical agents. The most widely used polymeric nanoparticles include, for instance, polylactides (PLA), polyglycolides (PGA), poly(lactide-co-glycolides) (PLGA), polyanhydrides, polycyanoacrylates (PC) and polycaprolactone (PCL). In general, polymeric nanoparticles have demonstrated many mechanisms through which the drug reaches the brain [31]. These mechanisms include one or more of the following:

1- Forming a high concentration gradient across the BBB by enhancing retention in the brain capillaries.
2- Endothelial transcytosis across the endothelium.
3- Opening of the tight junctions

B. Polymeric Micelles

Polymeric micelles are clusters of polymeric molecules that disperse in water and have a spherical shape and size of 10-100 nm [36]. They are formed through the self-assembly of graft or block copolymers in the selective solvent, owing

to the fact that, they have high thermodynamic and kinetic stabilities [37]. They act as perfect nanocarriers for photodynamic therapy (PDT) drugs. PDT is one of the very promising techniques used for the treatment of superficial tumors. Along with photosensitizing agents, polymeric micelles can respond to magnetic fields, as it can incorporate superparamagnetic iron oxide (SPIONS) nanoparticles [38]. This magnetically guided drug delivery system would decrease the drug dosage which in return decreases drug accumulation in normal tissue. Moreover, some polymeric micelles can respond to external stimuli such as light, pH, temperature and ultrasound [24].

Lihong *et al.,* have designed self-assembled polymeric micelles from cholesterol-conjugated poly(ethylene glycol) (PEG) that is anchored with transcriptional activator TAT peptide for delivery of ciprofloxacin as antibiotic. Herein, the presence of TAT promoted enhanced cellular uptake of astrocyte to micelles. Furthermore, these micelles showed promising results in crossing BBB providing a strategy for delivery of antibiotics to cross BBB [39]. In addition, Jiaojiao *et al.,* demonstrated that the oral delivery of vinpocetine loaded within mixed micelles composed of P_{123} and PEG_{2000}-PCL_{4000} in combination with borneol is a promising strategy for drug delivery to the brain across the BBB [40].

C. Dendrimers

Dendrimers got their name from the Greek word "Dendron" which means a "tree" [41]. They are branched polymers symmetric around the core and adopt a rounded three-dimensional morphology in water. Owing to their branched shape and the high control of surface functionality, they act as perfect carriers for many drugs at a time to the brain with high loading capacity and low toxicity [24,42].

Bhairavi *et al.,* showed that administration of convention cationic dendrimers is highly toxic. Thus, they designed novel dendrimers, with a slight cationic surface/neutral surface composed of (90% OH and 10% NH_2), and having the ability to cross BBB when injected through carotid artery. This method considered as an effective therapeutic strategy to the brain [43]. Moreover, Shafq *et al.,* have designed biodegradable and biocompatible dendrimer encapsulating flurbiprofen as a therapeutic drug for Alzheimer's disease (AD). This drug delivery system had the ability to cross BBB and to target the brain [44].

4 Role of Microglia in Pathogenesis of Brain Disorders

Since revolving, immune cells don't have the accessibility to the brain in physiological conditions, and the CNS owns a special immune system in which microglia are their stellar habitants[45]. Microglia, which are distributed along the parenchyma, are found in large numbers, and they compromise approximately 10-20% of the whole population of glial cells in the brain. They are usually referred to as "resting microglia" in the healthy diseased brain. Using two-photon microscopy *in-vivo*, the function of microglia in this resting state was determined, and they were shown to be constantly probing their immediate surroundings [46]. Microglia perpetually monitor their surroundings and act as a troubleshooter in innate immunity for controlling early infection. They also function as a classic macrophages but are different from other tissue macrophages through having a unique homeostatic phenotype in addition to the high regulation by the CNS microenvironment [47]. Microglia not only fights against invading microbes but also regulate the brain development, maintain neuronal networks by removing unwanted or repeated synapses, repair injuries, eliminate dead cells and protein aggregates as well as other soluble antigens that may threaten the CNS [48].

The functional capacity of microglia is mirrored by their morphology. For example, in the normal physiological conditions of the brain, microglia are in a quiescent shape showing a down regulating phenotype of arborized shape with short, exquisite and highly mobile processes that permit a larger surface area of tissue surveillance. Upon sensing pathogen invasion or tissue damage, they rapidly switch to the activated phenotype which is characterized by having huge branching processes, and hypertrophy of the cell body [49]. They also release exosomes and micro-vesicles (MVs) lifting the pro-inflammatory cytokines interleukin-1β (IL-1β), the IL-1β-processing enzyme caspase-1, and the P2X7 receptor to initiate secondary inflammatory responses and this process refers to the activation of microglia (Fig. 3).

It is worth to mention that the inflammation caused by reactive microglia propagates throughout the brain and called neuroinflammation. The term neuroinflammation includes the inflammation of both the central and peripheral nervous systems [50]. Microglia and neuroinflammation became highly linked, and neuroinflammation has been accused of being the initiator of neurodegenerative and neuropsychiatric diseases. Both categories of diseases are described by having aberrant thoughts, emotions, behaviors, and social interactions [51].

Recently, the number of people suffering from psychiatric and neurodegenerative diseases has so much increases. In this context, microglial cells may serve as the key therapeutic target which recently have been extensively studied in these conditions [52].

5 Nano drug Delivery Systems Targeting Microglia for Treatment of Brain Disorders

5.1 Neurodegenerative Diseases

Neurodegenerative diseases, through which not only physical health is stolen but also personality, memories and the ability to speak or even move, are the leading cause of

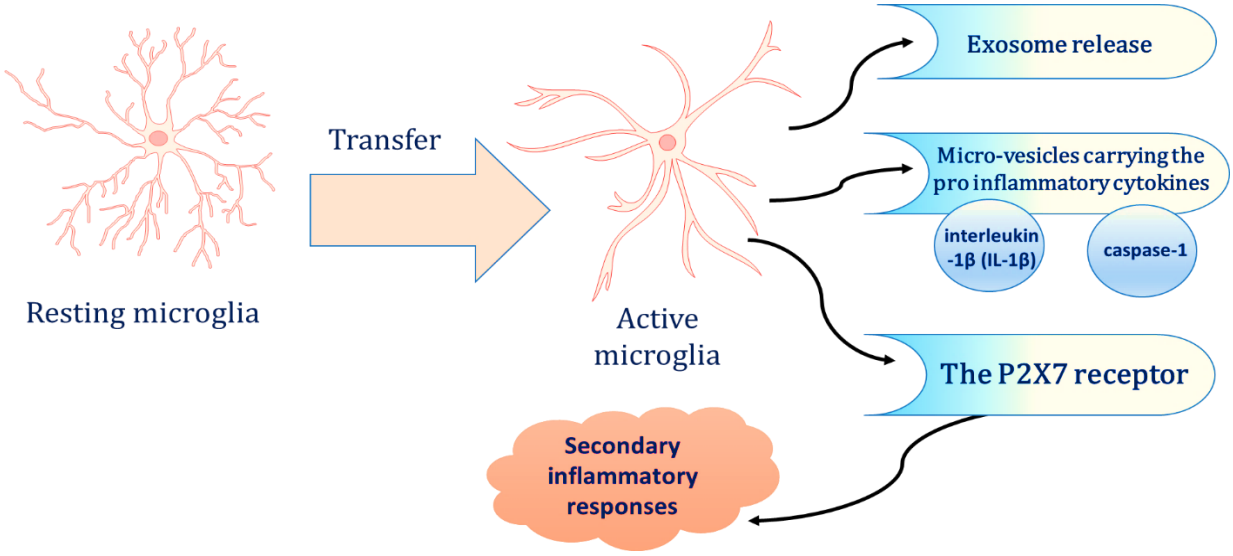

Fig. 3: A schematic illustration of the role of microglia in pathogenesis of brain diseases.

disability worldwide [53]. Up to date, neurodegenerative diseases, from Prion to Alzheimer disease had been totally unbeatable. Besides, all neurodegenerative diseases share the same devilish fate, although they are somehow different in their pathophysiology.

A. Alzheimer Disease

Today, Alzheimer's disease (AD) speaks for the most prevailing form of dementia. It commonly affects old people who are 65 years or older, however the pathology is thought to begin decades before the commence of the cognitive symptoms [54]. Before the clinical manifestation of AD, patients often exhibit signs of mild cognitive impairment (MCI). This disease is characterized by the accumulation of both neurofibrillary tangles and amyloid plaques in the brain [55]. All together with an innovative neurodegeneration that leads to memory loss. Moreover, AD is linked to an inflammatory status in the CNS which is not clear yet whether this inflammation is the lead or the consequence of the disease. Besides, most clues point to amyloid β (Aβ) as the purported cause, however, the underlying cause is still mostly unknown[56]. Herein, microglial mediate inflammatory response in the AD. Excessive microglial inflammation in AD induces a neuronal damage because of the overabundance of pro-inflammatory factors as the pro-apoptotic protein tumor necrosis factor (TNF)-α as well as reactive oxygen species (ROS) and nitric oxide (NO) [57].

The results of a recent study reported by Daniel A. Gonzalez-Carter *et al.* showed that microglia in AD can be targeted using silver nanoparticles (AgNPs) [58]. Besides, previous work by the same group has shown that microglial cells are able to internalize and degrade nano-sized materials, which means that microglia are the main cell type responsible for dealing with brain-penetrating nanomaterials such as AgNPs [59]. Understanding the mechanism through which microglia take up the AgNPs, for instance, and handle them opens the door for the prediction of the bioreactivity and biopersistence of AgNPs and other similar nanoparticles. AgNPs usually induce toxicity through releasing Ag^+ ions which interact with the cell membranes, DNA and thiol protein groups causing their damage [60].

Despite the fact that, whether Ag^+ ion sulphidation is evoked by AgNPs in microglial cells or not is not known, a hypothesis arose postulating that Ag^+ ions discharged from AgNPs after endocytosis by microglial cells promote the expression of H_2S-synthesizing enzymes, causing re-precipitation of the Ag^+ ions as insoluble Ag_2S, decreasing the toxicity of the AgNPs [61].

Alejandro *et al.,* have designed superparamagnetic iron oxide nanoparticles (SPIONS) which are biodegradable and biocompatible. These SPIONs entrapped siRNA to knockdown the expression of TREM2 and CD33 genes in microglia cells whose mutations are risk factors to develop AD. This study showed that exploitation of these nanoparticles to magnetic field allow rapid concentration of siRNA in the microglia cells [62]. Furthermore, Solberg *et al.,* have used anti amyloid-β (Aβ) conjugated to SPIONS in treatment of transgenic amyloid-β protein protein/presenilin-1 (AβPP/PS1) mice for one year. In this study *ex-vivo* measurements indicated that this type of treatment reduced microglial activation by 4.2- fold and 3.5-fold [63]. Moreover, Tafoya *et al.,* investigated the effect of anti-Iba-1-conjugated to superparamagnetic FePt-nanoparticles on Alzheimer's disease. They showed that these nanoparticles served to reveal the 3D distributions of both amyloid-β plaques and activated microglia [64].

B. Parkinson Disease

Unfortunately, Parkinson disease (PD) ranked two after AD as the most common neurodegenerative disease worldwide. In developed countries, PD affects almost 1% of aged populations, particularly of around 60 years old [65], and increases aggressively with age to reach about 4% of populations over 60 years [66].

PD commences by a minor rhythmic tremor, generally of a limb, then more symptoms arise during the progression of the disease due to the damage of dopaminergic neurons located in the substantia nigra pars compacta (SNpc) in mid brain and losing their projection to the striatum. These symptoms include; bradykinesia, gait disturbances, tremor at rest postural instability and developed rigidity. Moreover, patients lose control over their facial expressions [67]. These symptoms begin usually unilateral then later become bilateral, affecting the two sides of the body. PD targets non-motor areas of the brain as well, causing depression, insomnia and memory deficits. The disease is said to be quite advanced when the patient loses control of his voluntary movements, and around 80% of striatal dopamine has been lost.

It is worth to mention that the brain immune cells have shown an important role in the pathogenesis of PD. The first evidence against inflammation in PD resulting from a postmortem case in 1998 by McGeer and his colleagues who found the presence of activated microglia and T-lymphocytes as well as inflammatory enzymes as inducible nitric oxide synthase (iNOS) as well as cyclooxygenase 2 (COX2) in the SNpc of a PD patient [68].

Tiwari *et al.,* investigated the effect of nicotine-encapsulated poly(lactic-co-glycolic) acid nanoparticles against MPTP-induced parkinsonism. They founded that nicotine-encapsulated PLGA nanoparticles improved the endurance of TH-immunoreactive neurons and the number of fiber outgrowths. Furthermore, these nanoparticles increased the mRNA expression of TH, growth-associated protein-43 and neuronal cell adhesion molecules in the *in-vitro* model. Moreover, in the *in-vivo* model, it reduced TH immunoreactivity, levels of dopamine and its metabolites. Furthermore, it increased microglial activation, expression of GSTA4-4, iNOS, MT-III, HO-1, p53, and caspase-3, and the levels of nitrite and LPO [69]. In addition, Bennett *et al.,* used mucic acid-derivatized sugar-based amphiphilic nanoparticles for microglia targeting in PD. These nanoparticles decreased monomeric protein α-synuclein (ASYN) internalization and intracellular ASYN oligomer formation associated with microglial activation and diminished microglial neurotoxicity [70].

C. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a unique degenerative neurologic disease which is indicated by loss of both, neurons coming out of the cortex innervating brain stem and spinal cord (that are the upper motor neurons), and those which are coming from the brain stem and spinal cord innervating the muscles (that are the lower motor neurons) [71]. ALS is leading to paralysis and eventually death which usually occurs 3 to 5 years after the disease's diagnosis usually due to failure of the respiratory muscle. Men are more susceptible to the ALS (3.0 per 100.000 person /year) than do women (2.4 per 100.000 person/ year). The actual cause of ALS is not known in most patients, however some persons have familial disease that is linked to mutations in genes of multi functions, as roles in non-motor cells [72].

The clinical diagnosis of the ALS disease depends on the realization of hyper-reflexia, which is the deceleration of accelerated movements and increased muscle tone (upper motor neurons symptoms), in addition to the fasciculation and muscle wasting (lower motor neurons symptoms). Moreover, ALS progression leads to relentlessly progressive muscle weakness as well as failure of the respiratory muscle which ends by death [73].

It has been reported in several studies that neuroinflammation has a role in the degeneration of motor neurons. Increased activation of glial cells, especially microglia and astrocytes leads to the release of pro-inflammatory and hazardous neurotoxic agents which contribute to neurodegeneration [74].

Neuroinflammation can be realized in imaging studies in patients with ALS as well post-mortem samples of humans and rodent models of ALS-113,114. Astrocytes and microglial cells discharge a number of precarious and possibly neuroprotective factors. These data were confirmed by postmortem analysis of ALS patients and *in-vivo* imaging techniques as well as the high expression levels of translocator protein (TSPO), a good marker of enhanced activated microglia [75].

Usually, microglia are defined by two active phenotypes, M1 which is the classically activated or toxic phenotype, and M2 which represents the neuroprotective phenotype. Data suggested that during the progression of the disease, microglia are strongly converting to M1 phenotype, increasing the release of ROS and inflammation- inducing cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6 and decreasing the production of neurotrophic factors like insulin-like growth factor-1 (IGF-1) and IL-4 [76]. As a result, the neurotoxic factors discharged by these cells and the non-neuronal populations are attracting different therapeutic strategies. However, the inflammatory response in ALS is a convoluted phenomenon because of the conflicted effects of microglial activation and the downstream factors they produce.

5.2 Neuropsychiatric Diseases

It is worth mentioning that, a wide range of population are suffering from various psychiatric diseases worldwide, resulting in a remarkable socioeconomic burden. Mental health diseases negatively affect work performance. For example, patients suffering from bipolar disorder lost 65.5 as an average of their work days per year because of the illness. Likewise, patients experiencing major depressive disorder lost approximately 27.2 workdays. In addition to

having poor quality lives, patients with serious mental illness are at increased risk of premature death, where about 90% of all suicide cases per year around the world are correlated to different forms of mental illness [77].

Schizophrenia, major depressive disorder and bipolar disease are some types of neuropsychiatric disorders which have a multifactorial pathophysiology including genetic and environmental factors [78]. There is a growing amount of evidences that suggest the role of neuroinflammation in the pathophysiology of psychiatric disorder [79]. These evidences include the remarkable high levels of different inflammatory markers as cytokines, chemokines and their receptors in patients suffering from psychiatric disorders. Again, microglial cells which have a key role in neuroinflammation and pathophysiology of neuropsychological diseases become activated and change their morphology and function. Their activation induces the discharge of pro-inflammatory cytokines including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α causing neuronal death. Microglial cells can be activated by some activators including; P2X7 purinergic receptor (P2X7R) [80].

A. Schizophrenia

Schizophrenia is a destructive mental disorder which affects about 1% of the world population. The onset of the disease is generally in the late adolescence or early adulthood which forms a social and economic burden for patients, families and societies [81]. Schizophrenia is accompanied with abnormal structural brain connectivity. Studies showed that schizophrenia has neurodevelopmental origin, and the abnormal neurodevelopmental process together with the combination of environmental and genetic factors start long before the clinical symptoms of schizophrenia appear [82].

The clinical symptoms of schizophrenia are classified into positive symptoms which include hallucinations, delusions, disorganized speech, and negative symptoms such as lack of motivation, attentional and cognitive deficits as well as social withdrawal [83].

Up to date, the cause and pathophysiology of schizophrenia are not fully understood, and the collected data suggests that disruption of various neurotransmitter systems such as serotonin, gamma amino butyric acid, dopamine and glutamate may play an important role in the appearance of schizophrenic symptoms [84]. Besides, a growing data links the neuroinflammation to schizophrenia, and these evidences are based on the significant elevated levels of several pro-inflammatory cytokines in the serum. Moreover, there are increased serum and cerebrospinal fluid levels of S100B, which is a convenient marker for the annihilation of CNS tissue during different diseases including neurodegenerative disorders [85].

More data published by Doorduin and colleagues who compared the hippocampi of patients with schizophrenia to healthy controls, indicated the presence of neuro-inflammation in the focal region as well as elevated serum concentrations of interleukin (IL)-2, IL-6 and IL-8 after the onset of the disease [86].

As microglial activation and neuroinflammation are highly linked, some studies observed an increase in microglial density in brains of schizophrenic patients, however other studies reported no significant increase. Therefore, it can be suggested that there is no correlation between the density of microglia and its activity [86].

Recent morphological analysis in postmortem schizophrenic tissue showed signs of both microglial activation, microglial degeneration and brain attack by different immune cells in the posterior hippocampus. Confirming these data using animal models of schizophrenia, researchers reported an increased number of microglial activation that is characterized by reduced arborizations as well as microglial abnormalities.

If the activation of microglia helps in the pathophysiology of schizophrenia, then direct modulators of microglia function may be efficient in the treatment of psychotic disease [2,3,87]. Despite finding that that several antipsychotics can inhibit microglial activation, hepatic metabolism and rejection by blood brain barrier remains a major problem to face.

For that reason, researchers recently focused on using colloidal drug transporters such as micelles, emulsions, liposomes because preparation methods are much more straight forward and easy to maximize [88]. If nanoparticles could specifically target and modulate microglial function, the therapeutic strategy for schizophrenia will be taken to a high level.

B. Major Depressive Disorder

Major depressive disorder (MDD) is a common mental disorder that is characterized by clear-cut changes in mood that lasts at least two weeks. These changes in mood include loss of interest or pleasure, disrupted sleep and appetite, feelings of low self-worth, low energy as well as changes in cognition and poor concentration[89].

MDD usually occurs as a result of adverse life events, resembles the loss of specific person, relationship, object or health. Yet, it can occur without any apparent reason. It usually hits women about twice as men and it affects about 6% of the adult population worldwide each year [90].

MDD can become chronic or recurrent leading to significant impairment's in the patient's ability to take care of his/her everyday responsibilities. For that reason, depression is the second major contributor to chronic disease hardship as measured by "years lived with disability" MDD is linked to physical illness, surveys in general hospitals showed that around 10-20% of internal

medicine in- and outpatients suffer from so called 'depressive illnesses [91].

It's noteworthy to say that depression may increase the death rate for many physical diseases, there is a link between depression and mortality rate which have been reported among patients suffering from cancer, renal diseases, heart failure, diabetes and patients who passed by myocardial infractions and strokes [92].

MDD is linked to inflammation, and the inflammatory hypothesis of depression evolved 200 years ago, nominating MDD as a cytokine-mediated disorder [93]. It was shown by a population-based study that autoimmune diseases and prior severe infections increase the risk of developing MDD. In addition, mechanisms of inflammation in patients who are on cytokine treatments for hepatitis virus infection or cancer are relevant to depression. Lastly it was confirmed by meta-analyses that depressed patients show increased serum levels of cytokines as tumor necrosis factor (TNF) and IL-6 [92].

Evidences suggest that glial pathology is a salient aspect in MDD, specifically microglia the professional phagocytes of the CNS. In post-mortem human studies, higher magnitude of microglial activation was recognized in different brain areas including anterior cingulate cortex, pre-frontal cortex and hippocampus of patients who completed suicide [94]. However, the pathophysiological role of microglial activation has not been clearly identified, further studies are obliged to validate the link and understand the pathogenic mechanisms involved [93].

As the alteration of the monoaminergic transmission in the brain is the main reason of depression due to complex interaction of several factors, researchers for many years have focused on producing monoaminergic antidepressants such as selective serotonin and norepinephrine reuptake inhibitors (SNRI) and serotonin reuptake inhibitors (SSRI). However, the remission rate after the first trial of an antidepressant is <30%, that continues to decrease after a first antidepressant failure [95].

Moreover, the efficacy of the traditional antidepressant is confined owing to their inability to access the brain adequately from the systemic circulation because of the strong barriers of the brain which are the blood brain barrier (BBB) and cerebrospinal fluid (CSF). For that reason, scientists have been focusing on developing new ways for specific targeting of the brain. These new ways showed up as nanoparticle drug delivery [96]. Microglial targeting has been also another new way to tackle depression, as reported by Kwon *et al.*, that microglia-derived synaptic changes induced anti-depressive like behavior by using microglia-specific signal transducer and activator of transcription (STAT3) [97]. Trying to search the data base for a combination of both therapeutic strategies i.e.; specifically targeting microglia with nanoparticles, yields zero results So, in this review we recommend further research using both strategies to find an effective therapy against depression [98].

C. Autism (ASD)

Autism spectrum disorder (ASD), as stated in the international statistical classification of diseases and related health problem, is a pervasive developmental disorder. It is considered as a group of heterogeneous neurodevelopmental conditions based on the coexistence of early-onset difficulties in social attachment and interactions, stereotypic pattern of behaviors and interests as well as impaired language [99,100]. ASD usually affects males 2-3 times more than females and affected children are in need for comprehensive care and support from specialists in various fields [101,102]. It is now clear by evidence supported by several studies that autistic children are having ongoing neuro-inflammatory process in distinctive brain regions, and these neuroinflammation includes the microglial activation which constitutes the majority of brain cells, activation of inducible nitric oxide (NO)-synthase (i-NOS) and elevated expression and/or release of cytokines and chemokines as well [103]. It has been reported by several studies that increasing NO levels leads to a decline in natural killer cells function, which is obvious to be amended in children with ASD. On the other hand, increase in the activity of i-NOS causes reduction in glutathione (GSH) levels which has an antioxidant protective effect in neurons and so this would cause neurons to be impaired more easily. GSH depletion has been expressed as an important feature in autistic children [99].

Moreover, microglia were reported to be abnormally active in ASD patients. Owing to their role in modulating the assembly of axonal tracts and cortical networks during development and their role in pruning of extraneous dendrites during the postnatal period, they are susceptible to epigenetic alterations induced by gestational insults [104]. It is also suggested that the pathogenesis of ASD starts by a gestational insult which alters the fetal microglial function by epigenetic mechanism and that's how the disrupted microglia can't perform their normal roles in synaptic pruning and cortical organizations, which after all contributes to the classical symptoms of ASD [104].

The activation of the immune system also leads to the increased production of anti-phospholipid antibodies (APLAs). These antibodies are linked to the increased risk of blood clotting and have been found in plasma of autistic children of age range between 24-82 months and associated with their impaired behavior. Autism is not about different brain wiring but also the neuroinflammation process which is pathological characteristic of autism from childhood to adulthood [103].

Nanoparticles have been recently used in the treatment of ASD, especially gold nanoparticles as it has been suggested by Ghanizadeh, that both gold nanoparticles with lipoic acid administration can decrease the symptoms of autism by different antioxidant and anti-inflammatory

mechanisms. Moreover, these suggestions were validated by another study which found that the expression levels of antioxidant enzymes; catalase, glutathione peroxidase and superoxide dismutase and together with oxygen radical absorbance capacity increase with administration of gold nanoparticles in autistic mice [105]. To date, nobody has tried to target microglia using nanoparticles which might be another way to inform therapeutic interventions.

6 Conclusions

Nanoparticles and the other materials on the nano-scale, with their extremely small size are important to understand when addressing nanomedicine, as it allows many sorts of interactions or contacts between them and the living tissues, which are undoable with larger materials.

Nanoformulated drugs are characterized by having several physical advantages which may be lacking in the drug alone, such as increased stability rate/decreased physiologic clearance rates, reduced toxicity, improved solubility and improved clinical efficacy as well. Many types of nanoparticles have been developed to deliver the CNS drugs to the brain because they can pass through the BBB such as liposomes, micelles, nanogels, nanoemulsions, quantum dots, dendrimers, exosomes and polymers. Microglia, the immune resident of the brain are implicated in the pathophysiology of many psychiatric and neurodegenerative diseases. Getting advantage of this role, scientists are trying to target microglia using nanoparticles as a therapeutic intervention. However, microglia haven't been targeted in a broad range to cover all the neurological diseases, but we hope that our review will spot light on some of those diseases for further investigations.

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