Advanced prodrug approaches for neurodegenerative diseases

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Abstract

The prodrug technique is still one of the most effective ways to increase hydrophilic substances' medicinal, pharmacodynamic and pharmacokinetic properties. Prodrugs produced in current history have shown good pharmacokinetic characteristics, allowing for a more consistent release and fewer changes in plasma levels. Developing new prodrugs having a desirable ADME (Absorption Distribution Metabolism and Elimination) properties and that still can cross the Blood brain barrier (BBB) and pharmacologically active an appealing task for medicinal chemists. The loss of brain neuron activity characterizes neurodegenerative illnesses, resulting in progressive Gradual cognitive impairment (GCI). Some of the common neurodegenerative diseases are PD (Parkinson's disease), AD (Alzheimer's disease), MS (Multiple sclerosis), ALS (amyotrophic lateral sclerosis) & HD (Huntington's disease) are examples of neurodegenerative illnesses with a variety of etiologies and morphological and pathophysiological aspects. The current review is concerned with current advances in prodrug approaches for the treatment and prevention of the most prevalent neurological illnesses, as well as their absorption, selective CNS targeting and chemical and enzymatic stability.

Keywords: Alzheimer's disease, biotransformation, multiple sclerosis, prodrugs, pharmacokinetic.

1. Introduction

1.1 Prodrug

Albert was the first person to introduce the term "prodrug" in medicinal chemistry in 1958. Prodrugs are chemical compounds which are pharmacologically inert that undergo a biotransformation process converting into an active substance earlier than showing pharmacological effects (Benek et al., 2020). They are drugs that comprise precise innocuous groups which can alternate or eliminate undesirable properties of parent molecule (Albert, 1958).
In general, specialized enzymes primarily hydrolases, catalyze the metabolic change that turns the prodrug into the drug, and should ideally occur selectively at the target tissue to avoid undesired complication which can be released before, during, or after absorption (Sinkula; Yalkowsky, 1975). The main purpose of prodrug design is to overcome the variety of challenges in physicochemical, pharmaceutical, biopharmaceutical, and pharmacokinetic properties of the parent drug, which would otherwise prevent it from being used in clinical trials (Rautio et al., 2008). The prodrug concept has observed several applications in drug studies and development because it allows for the achievement of several contradictory biological and physicochemical goals (Han; Amidon, 2000).

There are a variety of ways to categorise prodrugs, these could be: (1) Therapeutic classes, such as antibacterial, anticancer, non-steroidal anti-inflammatory prodrugs (NSAIDs), antiviral, cardiovascular prodrugs, and so forth; (2) Esteric prodrugs, like bipartite, tripartite prodrugs and gene, virus-directed enzyme and glycosidic prodrugs are examples of chemically linked or moiety or carriers connected to active drug; (3) Prodrugs which increase site-specificity, skip first-pass metabolism and improve absorption are few examples of beneficial strategic ways (Bianchi et al., 2021).

1.2 Neurodegenerative diseases

The loss of brain neuron activity is characteristics of Neurodegenerative diseases, resulting in gradual cognitive impairment (GCI). Neurodegenerative disorders like Dementia, Alzheimer's disease are increasing, and around 17.2 million people worldwide are suffering from them. If the risk factors are reduced to 10%-25%, it can prevent 1.1–3.0 million cases of Alzheimer's disease globally (Saydoff i et al., 2003). The function of epigenetic variables in the development of neurodegenerative illness has been extensively studied, with evidence of the importance of DNA and histone changes, as well as non-coding RNA, in the pathogenesis of these diseases (Jellinker, 2003).

Parkinson's disease (PD), Huntington's diseases (HD), Alzheimer's disease (AD), Multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) are some neurodegenerative diseases with diverse etiologies and morphological and pathophysiological aspects. These conditions are complex and exhibit neuropathological markers such as: (a) mitochondrial dysfunctions and impaired bioenergetics; (b) neuro-inflammatory processes (c) Impaired protein breakdown and aggregation due to abnormal protein dynamics; (d) Free radical formation and oxidative stress (Jellinker, 2003).

Although the exact chronology of operations is difficult to determine, oxidative damage to the brains has been demonstrated to be one of the earliest clinical signs. The oxidative stress is caused by imbalance between the increased generations of reactive nitrogen species (RNS), reactive oxygen species (ROS), and the anti-oxidative defense systems cause oxidative and nitrosative stress ( Valko et al., 2007). ROS are regulatory intermediates that modulate cellular functions at low levels, and they cause neuronal membrane injury at higher concentrations. The hydrogen peroxide (H2O2), superoxide anion (O2•−) and hydroxyl radical (HO•) are the major ROS involved in neurodegeneration. Nitric oxide (NO) and other ROS can combine with oxygen to form peroxynitrate (NO3•−), a potent oxidant can decompose to form HO• (Melo et al., 2011).

Cells generally use enzymes Glutathione (GSH) peroxidase, Cu/Zn reductase enzyme, catalase enzyme, methionine sulfoxide reductase enzyme and Manganese superoxide dismutase (MSD) and low molecular-weight antioxidants (vitamin E, and ascorbate) against free radicals. When the antioxidant defense network fails, macromolecules including proteins, lipids, and DNA are destroyed, resulting in apoptosis or cell death (Lardenoije et al., 2018).

2. Literature review

2.1 Prodrug treatment strategies for various neurodegenerative diseases

2.1.1 Alzheimer’s disease

Alzheimer's disease (AD) is a neurological illness among the elderly which causes attention problems, cognitive and memory loss. It is most frequent kind of dementia among neurodegenerative diseases. Histological alterations associated with the disease include extracellular β-Amyloid (Aβ) deposits and intracellular neurofibrillary tangles (NFTs) (McBride et al., 2004). Plaques or accumulation/aggregation of β-Amyloid (Aβ) peptides 40-42 amino acids in length is one of the hallmarks of Alzheimer's disease. They are made by the β-secretase (BACE) enzyme proteolytically cleaving the Aβ primordial polypeptide (AβPP) and subsequently the
γ-secretase enzyme. The production of Aβ oligomers and amyloid plaques as a result of this is considered to play a key role in neuronal degeneration and, eventually, cognitive failure (Lima et al., 2018). Pro-inflammatory mediators like interleukins (IL)-1α, interleukins-1β, interleukins-6, cytokines, and tumor necrosis factor (TNF-α) are also linked to plaques. The tau (τ) protein linked with microtubules is abnormally phosphorylated in the AD brain. These τ-proteins induce the microtubule system to break down, resulting in neuronal malfunction and degeneration. Cognitive impairment, neural inflammation, and neuronal death are primary symptoms to diagnose AD (Athar et al., 2021).

2.1.2 Anti-Alzheimer’s prodrugs

The two categories of medications currently used for the treatment of Alzheimer's disease are acetylcholinesterase (AChE) inhibitors and N-methyl-D-aspartate (NMDAR) receptor antagonists. The former impede acetylcholinesterase activity and boosts acetylcholine level inside the CNS restoring cognitive function. The latter prevents glutamate toxicity caused by NMDA over-activation. Only a few of the symptoms of Alzheimer's disease can be alleviated with these drugs (Corbett; Ballard, 2012). The β-amyloid theory has governed the pathophysiology of Alzheimer's disease. Efforts to target conventional routes, on the other hand, have been continuously unproductive over the last decade. As a result, more powerful disease-modifying treatments and cognitive impairment medications are needed to delay the onset or prevent the Alzheimer's disease (Giacobini; Gold, 2013).

2.1.3 Prodrug of 7,8-dihydroxyflavone (7,8-DHF)

Growth factors like Neurotrophins regulate the viability, differentiation, and development of neurons. The cognate Tropomyosin receptor kinase B (TrkB) receptors are where neurotrophins exercise their trophic effects. The expression of brain-derived neurotrophic factors (BDNF) in Alzheimer’s affected brains is seen to be reduced. Thus 7, 8-dihydroxyflavone (7,8-DHF), acts as a powerful BDNF mimetics and TrkB agonist, having promising anti-Alzheimer’s effect. But 7,8-DHF, on the other hand, has low pharmacokinetic (PK) profile and oral bioavailability. Chen C, et al. synthesized number of 7,8-DHF derivatives by modifying the catechol ring of the parent molecule with an ester or carbamate group from which prodrug R13 (Figure 1) exhibited positive qualities and restored cognitive impairments in an AD mice model depending on the dose, and it increased brain exposure of prodrug and bioavailability. ALZ-801 (Figure 2) is a valine-conjugated tramiprosate prodrug developed by Hey et al. (2018) that can be taken orally. ALZ-801 is a reformulated tramiprosate prodrug that maintains tramiprosate's effectiveness while enhancing oral PK variability and gastrointestinal tolerability. ALZ-801 was well tolerated in the study, with no serious or major adverse events or abnormal laboratory test results. ALZ-801 produced dose-dependent peak plasma concentrations (Cmax) and AUC tramiprosate exposures equal to oral tramiprosate, but with much lower inter-subject variance and a prolonged elimination half-life. ALZ-801 exhibited greater oral safety and tolerability when given as a capsule or tablet. With considerably enhanced PK characteristics when compared to oral

2.1.4 Prodrug of tramiprosate

Tramiprosate is a small-molecule aggregation inhibitor and anti-oligomer for Alzheimer's disease. Tramiprosate inhibits the formation of β-amyloid oligomers through a multi-ligand wrapping mechanism of action that stabilises Aβ42 monomers, inhibiting the development of oligomers and subsequent aggregation. Tramiprosate has drawbacks of substantial inter-subject pharmacokinetic (PK) variability, which was likely owing to extensive gastrointestinal metabolism and a mild-to-moderate incidence of vomiting and nausea. ALZ-801 (Figure 2) is a valine-conjugated tramiprosate prodrug developed by Hey et al. (2018) that can be taken orally. ALZ-801 is a reformulated tramiprosate prodrug that maintains tramiprosate's effectiveness while enhancing oral PK variability and gastrointestinal tolerability. ALZ-801 was well tolerated in the study, with no serious or major adverse events or abnormal laboratory test results. ALZ-801 produced dose-dependent peak plasma concentrations (Cmax) and AUC tramiprosate exposures equal to oral tramiprosate, but with much lower inter-subject variance and a prolonged elimination half-life. ALZ-801 exhibited greater oral safety and tolerability when given as a capsule or tablet. With considerably enhanced PK characteristics when compared to oral
tramiprosate in healthy individuals and elderly volunteers (Hey et al., 2018).

Figure 2. Chemical structure of ALZ-801. Source: Authors, 2023.

2.1.5 Prodrug of memantine
Memantine, a hydrogen sulphide donor has recently received a lot of interest because of its neuroprotective properties and anti-inflammatory in the brain. Sestito et al. (2018) replaced memantine's independent amine group with an isothiocyanate and made a new chemical entity called memit (Figure 3), which was then examined in vitro to see if it retained the "original drug’s" pharmacological profile while continuing to be a source of H₂S in the CNS. Memit produced memantine by using a cysteine-mediated method to release H₂S. Memit is a novel chemical which inhibits self-aggregation of Aβ(1-42) and acted as a cytoprotector against damage induced by oligomer in both rat microglial cells and neurons of human (Sestito et al., 2018).

Figure 3. Structures of memantine and the relative H₂S-donor hybrid memit. Source: Authors, 2023.

2.1.6 Peptide based prodrugs
Carnosine (Figure 4) is a dipeptide of β-alanyl and L-histidine and has potential to prevent amyloid aggregation and deposition in animal models of neurodegenerative illnesses, as well as influence macrophage and microglia activity. The anti-inflammatory property of carnosine is the one that has recently received the most emphasis. Carnosine has recently been shown to suppress astrocyte stimulation and inflammatory cytokine interferon- (IFN-γ) release, in a mouse model (C57BL/6) having subcortical ischemic vascular dementia, the mice with permanent closure of the right unilateral common carotid arteries), this resulted in neuroprotection (Caruso et al., 2019).

Figure 4. Structure of L-Carnosine. Source: Authors, 2023.

2.1.7 Amidated and ibuprofen-conjugated kyotorphins
Kyotorphin (KTP) is endogenous analgesia and anti-inflammatory dipeptide with a potential neuromodulator and neuroprotector activity. KTP-amide (KTP–NH₂) and KTP–NH₂ coupled to ibuprofen (IbKTP–NH₂), two recently developed KTP derivatives, have been suggested to increase KTP brain targeting (Satos et al., 2016). KTP is thought to have neuromodulatory and neuroprotective effects in addition to analgesia. According to the findings, KTP analogues minimized cognitive deficits and restored neurodegeneration in the hippocampus CA1 area produced by chronic cerebral hypoperfusion. IbKTP–NH₂ was also discovered to be more effective than
KTP–NH₂ in restoring normal brain abilities (Nazrenko et al., 1999).

Figure 5. Chemical structure of Ibuprofen-Conjugated Kyotorphins. Source: Authors, 2023.

2.1.8 NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)

Are types of medication which relieves pain, prevents blood clots, suppresses fever in larger dosages and reduces inflammation. The activity of cyclo-oxygenase enzymes is inhibited by NSAIDs (COX 1 & COX 2). These enzymes are involved in the manufacture of essential biological mediators in cells, like prostaglandins and thromboxanes, which are implicated in blood clotting and inflammation. NSAIDs are divided into two categories: Non-selective COX inhibitor like Diclofenac, Ibuprofen, Flurbiprofen, Indomethacin, Aspirin and selective COX-2 inhibitors like Celecoxib, Etoricoxib, Parecoxib (Mannila et al., 2005).

According to epidemiological research, alleviated risk of AD and PD were observed in patients with a history of prolonged NSAID usage (Novakova et al., 2014). The persistent inflammatory response in senile plaques leads to neuronal degradation processes, according to a large body of evidence. Furthermore, in the frontal cortex of the AD brain, the expression of cyclo-oxygenase (COX-2) is elevated, which catalyzes the manufacture of inflammatory mediators (Pasinetti; Aisen, 1998).

Many researchers have been inspired by the idea that NSAIDs, which suppress COX-2 activity, prevent neurodegeneration in Alzheimer's disease. NSAIDs distribution into the CNS is often limited, it is critical to design a delivery method for NSAIDs so that they may be taken up by the brain more efficiently. In randomized clinical trials, NSAIDs appear to be ineffective in lowering the rate of conversion of mild cognitive impairment (MCI) to dementia. According to a study that revealed contradictory results, NSAIDs appear to be ineffective in lowering the rate of conversion of MCI to dementia in randomized clinical trials (Deguchi et al., 2000).

2.2 Parkinson's disease

Parkinsonism is a CNS progressive disease and neurological disorder characterized by loss of dopaminergic neurons connections, especially in two parts of the brain: the locus coeruleus, which regulates psychological function, and the Substantia Nigra pars compacta (SNpc), which regulates motor function (Poewe et al., 2017). Lewy bodies are protein agglomerations lodged in the cytoplasmic part of dying neurons. They signal that the degenerative process has started (Xilouri et al., 2012). In PD patients cholinergic and serotonergic dysfunctions, as well as anatomical deficiencies, such as the hippocampus and cortical atrophy, were found. In PD patients muscarinic and neuromuscular and motor receptors are also shown to be reduced, and results in cognitive and motor deficits (Muller; Bohnen, 2013). The 5-hydroxytryptamine (5-HT) and its metabolites level in PD brain is found to be low in comparison to the normal brain. PD symptoms can be described in a trio of disorders: rigidity, tremor and difficulty in passive and active movement. The neurons of serotonin in striatum (putamen and caudate) found to be increased in PD patients (Savic a et al., 2013).

Despite of our recent advancements in the pathogenesis understanding of PD, getting the drugs pass through the BBB to the CNS remains a big hurdle. Levodopa (LD) is accepted as the standard drug for the treatment of PD. Prodrugs that combine one or more strategies to improve BBB penetration have made significant progress (Kianirad; Simuni, 2013). The use of prodrugs in conjunction with medication delivery devices has recently been successful strategy for brain targeting. The carrier's enzymatic & chemical protection, together with the prodrug's ability to penetrate the BBB barrier, has allowed for sustained and slow release, improving disease control and lowering plasma fluctuations (Marsden et al., 1973). Molecules used to treat neurodegenerative diseases like Parkinson's disease can enter the BBB using carrier-mediated transporters like GLUT1, CAT1, MCT1, CNT2&
LAT1, passive diffusion, receptor-mediated transporters, which includes leptin receptors, transferrin, and insulin & endocytosis (Muller, 2015).

2.2.1 Anti-Parkinson prodrugs

2.2.1.1 Dopamine (DA) prodrug

DA has a very strong LAT1 transporter affinity in the brain of rat. Tutone M et al. discovered and produced dopamine-amino acid prodrugs in 2016. To make the equivalent prodrugs, amino acids like L-leucine, L-tryptophan & L-phenylalanine, attached to the Dopamine amino group. Prodrugs 6d–6f were more hydrophobic than prodrugs 6a-6c, with Log D values > 0; nevertheless, their stability was less in human plasma having half life (t1/2) = 2 h and brain homogenate having half life (t1/2) = 3 h. The Dopamine prodrugs 6a to 6f are promising candidates for additional in vivo testing (Tutone et al., 2016).

Figure 6. Dopamine prodrugs. Source: Authors, 2023.

2.2.1.2 L-Dopa (LD) prodrugs

To address the LD bioavailability issue and peripheral metabolism, a water-soluble prodrug LD prodrug DopAmide (prodrug, Figure 7) was synthesized by amidation of the LD carboxylic group which has more extended half-life (t1/2 = 4.1 h 0 in rats than LD (t1/2 = 2.9 h). Furthermore, in vivo studies on rats with 6-hydroxy-dopamine infracted plasma levels demonstrated that the level of L-Dopa in plasma were sustained for a longer length of time after DopAmide therapy than after L-Dopa (Figure 8) treatment. Prodrug 7 when used for the treatment of 6-hydroxydopamine (6-OHDA)-infracted brains led in greater DA activity than LD therapy (approx. 35 percent rotations in total), showing that DA release is effective over time. Additionally, by providing a regular DA release, prodrug 8 reduced fluctuations (Atlas, 2016).

Figure 7. XP21279. Source: Authors, 2023.

8: R1 = R2 = R3 = R4 = H; R5 = NH2
9: R1 = R3 = R4 = H; R2 = P(O)(OH)2; R5 = OH
10: R1 = R2 = R4= H; R3 = P(O)(OH)2; R5= OH
11: R1= R4= H; R2 = R3 = P(O)(OH)2; R5 = OH
12: R1 = R3 = R4 = R5 = H; R2 = Ph
13: R1 = R2 = R3 = Me; R4 = R5 = H
14: R1 = Me; R2R3 = c-Hexyl; R4 = R5 = H
15: R1 = Me; R2R3 = c-Pentyl; R4 = R5 = H
16: R1= Me; R3= c-Hexylmethyl; R2 =R4=R5 = H
17: R1 = Bn; R2 = R3 = Me; R4 = R5 = H
18: R1 = i-Pr; R2 = R3 = Me; R4 = R5 = H
19: R1 = c-Hexyl; R2 = R3 = Me; R4 = R5 = H
20: R1 = i-Pentyl; R2 = R3 = Me; R4 = R5 = H
21: R1 = R2 = R3 = Me; R4 = R5 = Ac
22: R1 = Me; R2 R3 = c-Hexyl; R4 = R5 = Ac
23: R1 = Me; R2 R3 = c-Pentyl; R4 = R5 = Ac
Further the phosphate groups were conjugated with catechol group to create Levodopa phosphate prodrugs (prodrugs 9 to 11), which increased water stability and solubility. Prodrugs 10 and 11 have higher solubilities by 67 and 55 times, respectively, comparatively to the LD solubility. Furthermore, in a pharmacokinetic investigation on rats, the in-vivo prodrugs conversion was assessed. The phosphate prodrug hydrolyzed into LD completely after 24 hours, 66% of prodrug 9 converted to prodrugs 10 and 11. Zhou et al. (2010) used non-natural amino-acids to synthesize dipeptide LD prodrugs 13 to 27. The antiparkinson effects of prodrugs were tested 6-OHDA-lesioned rats, drug administered orally. The produg 18 containing amino acidic moiety 2,3-dimethylglycine, was found to be most active, with a hundred and six percent AUC activity and a 149% peak activity of LD. To corroborate these preliminary findings, more in vivo trials are required (Zhou et al., 2010).

2.2.1.3 Rasagiline prodrug
Rasagiline is a MAO-B inhibitor often prescribed for Parkinson's disease. It decreases oxidative stress and enhances synaptic DA concentrations at the same time. However, it has a low oral bioavailability of 36% and a short elimination half-life of 0.6–2 h. Fernández et al. (2012) designed and synthesized a method for controlled release of parenteral administration of the prodrug 33 rasagiline mesylate (Figure 9) in 2012. The carrier released 62.3 g per day per 20 mg microspheres in-vitro, followed by a two-week zero-order release with constant rate (Fernandez et al., 2012).

2.2.1.4 Prodrugs of Norepinephrine
The most common non-motor clinical manifestations associated with the Parkinson's disease is neurogenic orthostatic hypotension. It is produced by inappropriate generation of Norepinephrine (Figure 10) responses to postural alterations. Droxidopa is transformed to the sympathetic neurotransmitter through decarboxylation when taken orally. Goldstein et al. (2011) in 2011 investigated the effects of combination of L-Dihydroxyphenylserine (DOPS) with entacapone or carbidopa on metabolic destiny, hence it boosted the prodrug's action; nevertheless, no significant differences were found across treatments (Goldstein et al., 2011).
Figure 10. Norepinephrine prodrug (Prodrug 34). Source: Authors, 2023.

As persons with Parkinson's disease age, they are more likely to develop dementia, which causes significant morbidity and mortality in 80–90% of cases. The causes of Parkinson's disease are unknown; however, insulin resistance has recently been revealed, implying a relationship between glucose metabolism and neurodegeneration (Table 1) (Ashraghi et al., 2016).

Table 1. Prodrugs for the treatments of various neurodegenerative diseases.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure</th>
<th>Mechanism</th>
<th>Disease</th>
<th>Treatment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen and aromatic amino acid pro-moiety</td>
<td><img src="image" alt="Structure" /></td>
<td>Non-selective COX-inhibitor</td>
<td>Alzheimer's disease</td>
<td>(Tampio et al., 2020).</td>
<td></td>
</tr>
<tr>
<td>Amino acid conjugated indomethacin</td>
<td><img src="image" alt="Structure" /></td>
<td>Non-selective COX-inhibitor</td>
<td>Alzheimer's disease</td>
<td>(Roy et al., 2014).</td>
<td></td>
</tr>
<tr>
<td>L-ascorbic acid-prodrugs of ibuprofen</td>
<td><img src="image" alt="Structure" /></td>
<td>L-ascorbic acid as anti-oxidant and ibuprofen, anti-inflammatory</td>
<td>Alzheimer's disease</td>
<td>(Pignatello et al., 2008).</td>
<td></td>
</tr>
<tr>
<td>Prodrugs of naproxen coupled with dimethylamino moiety.</td>
<td><img src="image" alt="Structure" /></td>
<td>Non-selective COX-inhibitor</td>
<td>Alzheimer's disease</td>
<td>(Zhang et al., 2012).</td>
<td></td>
</tr>
<tr>
<td>D-glucose derivative of ibuprofen</td>
<td><img src="image" alt="Structure" /></td>
<td>Non-selective COX-inhibitor</td>
<td>Alzheimer's disease</td>
<td>(Chen et al., 2009).</td>
<td></td>
</tr>
<tr>
<td>Fluribiprofen(FLU)-lipo aminoacids (LAA) promoiety</td>
<td><img src="image" alt="Structure" /></td>
<td>Aβ aggregation inhibitor.</td>
<td>Alzheimer's disease</td>
<td>(Marsden et al., 1973).</td>
<td></td>
</tr>
<tr>
<td>Carbidopa Sinemet (in combination with L-Dopa)</td>
<td><img src="image" alt="Structure" /></td>
<td>Peripherally inhibitor of aromatic amino acid decarboxylase (AADC)</td>
<td>Parkinson's disease</td>
<td>(Rinne et al., 1979).</td>
<td></td>
</tr>
</tbody>
</table>
Benserazide Madopar (in combination with L-Dopa)  
Peripherally active inhibitor of AADC  
Parkinson's disease (Brooks et al., 2003).

Diphenhydramine Benadryl  
Anticholinergic agent  
Parkinson's disease (Gonzalez et al., 2009).

Source: Authors, 2023.

3. Conclusions
Prodrug technique is a useful tool for targeting medications to the brain with low water solubility, improving low distribution to target sites, minimizing enzymatic metabolism, improving adsorption, pharmacokinetic and pharmacodynamic features. However, there are several limitations to the prodrug technique like, dispersion of lipophilic prodrugs or prodrug bioconversion by enzymes of plasma at early stages, which can be addressed by nanotechnology methods that target and deliver the unmodified prodrug to the central nervous system, selectively. A delivery system of drug combined with prodrug technique could be an effective way to target and deliver drugs to the brain to prevent or treat the neurodegenerative diseases.

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5. Authors’ Contributions

6. Conflicts of Interest
No conflicts of interest.

7. Ethics Approval
Not applicable.

8. References


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