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.

Abordagens avançadas de pró-fármacos para doenças neurodegenerativas

Resumo

A técnica de pró-fármacos ainda é uma das formas mais eficazes de aumentar as propriedades medicinais, farmacodinâmicas e farmacocinéticas de substâncias hidrofílicas. Os pró-fármacos produzidos na história atual, mostraram boas características farmacocinéticas, permitindo uma liberação mais consistente e menos alterações nos níveis plasmáticos. Desenvolver novos pró-fármacos com propriedades ADME (Metabolismo e Eliminação de Distribuição de Absorção) desejáveis e que ainda possam atravessar a barreira hematoencefálica (BBB), e ser farmacologicamente ativos, é uma tarefa atraente para os químicos medicinais. A perda da atividade dos neurônios cerebrais caracteriza doenças neurodegenerativas, resultando em comprometimento cognitivo gradual progressivo (GCI). Algumas das doenças neurodegenerativas comuns são DP (doença de Parkinson), DA (doença de Alzheimer), EM (Eclerose Múltipla), ELA (Esclerose Lateral Amiotrófica) e DH (doença de Huntington), são exemplos de doenças neurodegenerativas com uma variedade de etiologias e alterações morfológicas e aspectos fisiopatológicos. A revisão atual está preocupada com os avanços atuais nas abordagens de pró-fármacos para o tratamento e prevenção das doenças neurológicas mais prevalentes, bem como sua absorção, direcionamento seletivo do SNC e estabilidade química e enzimática.

Palavras-chave: doença de Alzheimer, biotransformação, esclerose múltipla, pró-fármacos, farmacocinética.

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 (H_2O_2), superoxide anion (O^{2-}) and hydroxyl radical (HO•) are the major ROS involved in neurodegeneration. Nitric oxide (NO) and other ROS can combine with oxygen to form peroxynitrite (NO^{3-}), 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 neutotrophic 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. Long term oral treatment of R13 enhanced TrkB signaling and prevents pathogenic cleavage of amyloid precursor proteins (APP) (Chen et al., 2018).

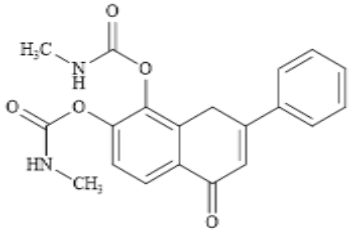


Figure 1. Chemical structure of R13. Source: Authors, 2023.

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 grater 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).

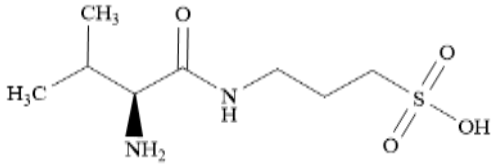


Figure 2. Chemical structure of ALZ-801. Source: Authors, 2023.

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 H_2S in the CNS. Memit produced memantine by using a cysteine-mediated method to release H_2S. 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).

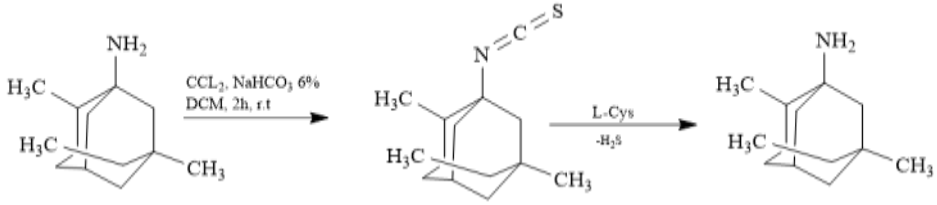


Figure 3. Structures of memantine and the relative H_2S-donor hybrid memit. Source: Authors, 2023.

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).

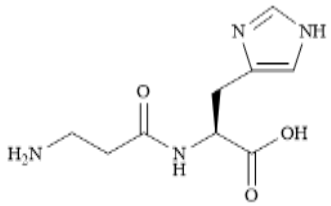


Figure 4. Structure of L-Carnosine. Source: Authors, 2023.

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–NH_2) and KTP–NH_2 coupled to ibuprofen (IbKTP–NH_2), 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–NH_2 in restoring normal brain abilities (Nazrenko et al.,1999).

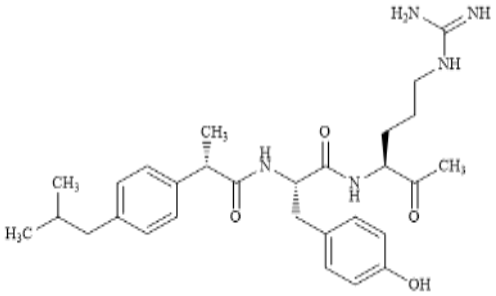


Figure 5. Chemical structure of Ibuprofen-Conjugated Kyotorphins. Source: Authors, 2023.

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 (Savica 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).

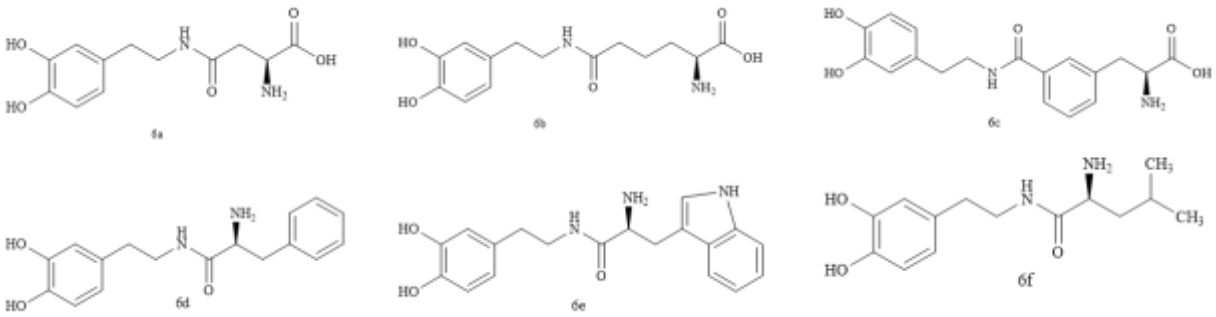


Figure 6. Dopamine prodrugs. Source: Authors, 2023.

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)-lnfracted 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).

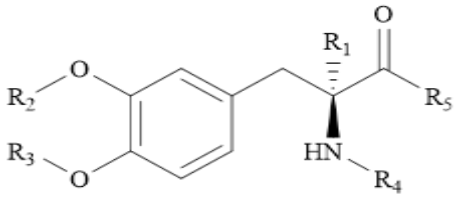


Figure 7. XP21279. Source: Authors, 2023.

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-Penthyl; 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

24:R1=Me; R2=H;R3=c-Hexylmethyl;R4=R5= Ac

25: R1 = R4 = R5 = H; R2 = R3 = Me

26: R1 = H; R2 = R3 = Me; R4 = R5 = Ac

27: R1 = R4 = R5 = H; R3 = Bn; R2 = Me

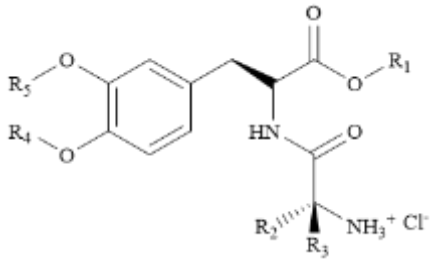


Figure 8. LD prodrugs. Source: Authors, 2023.

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 prodrug 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).

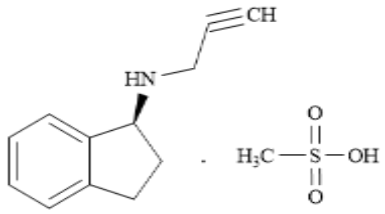


Figure 9. Rasagiline prodrug (Prodrug 33). Source: Authors, 2023.

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-Dihydroxyophenylserine (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).

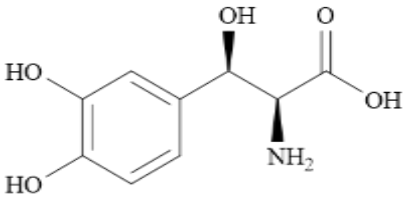
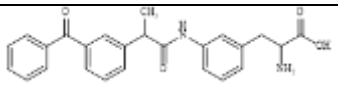
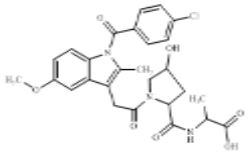
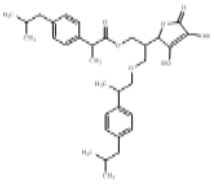
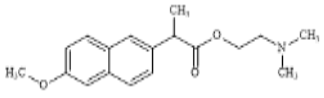
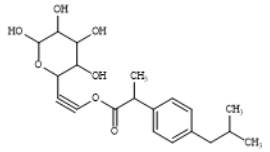
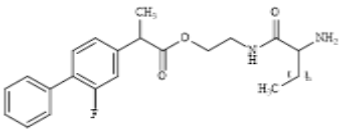
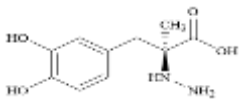
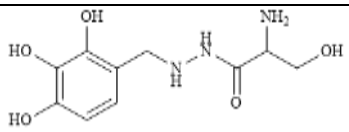
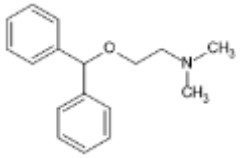


Figure 10. Norepinephrine prodrug (Prodrug 34). Source: Authors, 2023.

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.

Drug	Structure	Mechanism	Disease Treatment	References
Ketoprofen and aromatic amino acid pro-moiety		Non-selective COX-inhibitor	Alzheimer's disease	(Tampio et al., 2020).
Amino acid conjugated indomethacin		Non-selective COX-inhibitor	Alzheimer's disease	(Roy et al., 2014).
L-ascorbic acid-prodrugs of ibuprofen		L-ascorbic acid as anti-oxidant and ibuprofen, anti-inflammatory	Alzheimer's disease	(Pignatello et al., 2008).
Prodrugs of naproxen coupled with dimethylamino moiety.		Non-selective COX-inhibitor	Alzheimer's disease	(Zhang et al., 2012).
D-glucose derivative of ibuprofen		Non-selective COX-inhibitor	Alzheimer's disease	(Chen et al., 2009).
Fluribiprofen(FLU)-lipo aminoacids (LAA) promoiety		Aβ aggregation inhibitor.	Alzheimer's disease	(Marsden et al., 1973).
Carbidopa Sinemet (in combination with L-Dopa)		Peripherally inhibitor of aromatic amino acid decarboxylase (AADC)	Parkinson's disease	(Rinne et al., 1979).

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. Auhors' Contributions

Rashu Raju: project development, research, data compilation, submission, corrections and publication. *Anjali Nayak*: research, data compilation and corrections. *Paramita Das*: research, data compilation and corrections. *Anmol Gajmer*: research, data compilation and corrections. *Ramya A.*: research, data compilation and corrections. *Tejaswani, R.*: research, data compilation and corrections.

6. Conflicts of Interest

No conflicts of interest.

7. Ethics Approval

Not applicable.

8. References

Albert, A. (1958). Chemical aspects of selective toxicity. *Nature*, 182(4633), 421-423. https://doi.org/10.1038/182421a0

Athar, T., Al Balushi, K., & Khan, S. A. (2021). Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease. *Molecular Biology Reports*, 48(7), 5629-5645. https://doi.org/10.1007/s11033-021-06512-9

Atlas, D. (2016). DopAmide: novel, water-soluble, slow-release l-dihydroxyphenylalanine (l-DOPA) precursor moderates l-DOPA conversion to dopamine and generates a sustained level of dopamine at dopaminergic neurons. CNS Neuroscience & Theraoeuthics, 22(6), 461-467. https://doi.org/10.1111/cns.12518

Ashraghi, M. R., Pagano, G., Polychronis, S., Niccolini, F., & Politis, M. (2016). Parkinson's disease, diabetes and cognitive impairment. *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery*, 10(1), 11-21. https://www.ingentaconnect.com/content/ben/emi/2016/00000010/00000001/art00004

Benek, O., Korabecny, J., & Soukup, O. (2020). A perspective on multi-target drugs for Alzheimer's disease. *Trends in Pharmacological Sciences*, 41(7), 434-45. https://doi.org/10.1016/j.tips.2020.04.008

Bianchi, V. E., Herrera, P. F., & Laura, R. (2021). Effect of nutrition on neurodegenerative diseases. A systematic review. *Nutritional neuroscience*, 24(10), 810-834. https://doi.org/10.1080/1028415X.2019.1681088

Brooks, D. J., & Sagar, H. (2003). Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind, six month study. *Journal of Neurology, Neurosurgery & Psychiatry*, 74(8), 1071-1079. http://dx.doi.org/10.1136/jnnp.74.8.1071

Caruso, G., Caraci, F., & Jolivet, R. B. (2019). Pivotal role of carnosine in the modulation of brain cells activity: Multimodal mechanism of action and therapeutic potential in neurodegenerative disorders. *Progress in Neurobiology*, 175, 35-53. https://doi.org/10.1016/j.pneurobio.2018.12.004

Chen, Q., Gong, T., Liu, J., Wang, X., Fu, H., & Zhang, Z. (2009). Synthesis, *in vitro* and *in vivo* characterization of glycosyl derivatives of ibuprofen as novel prodrugs for brain drug delivery. *Journal of Drug Targeting*, 17(4), 318-328. https://doi.org/10.1080/10611860902795399

Chen, C., Wang, Z., Zhang, Z., Liu, X., Kang, S. S., Zhang, Y., & Ye, K. (2018). The prodrug of 7, 8-dihydroxyflavone development and therapeutic efficacy for treating Alzheimer's disease. *Proceedings of the National Academy of Sciences*, 115(3), 578-583. https://doi.org/10.1073/pnas.1718683115

Corbett, A, & Ballard, C. (2012). New and emerging treatments for Alzheimer's disease. *Expert Review of Neurotherapeutics*, 12(5), 535-543. https://doi.org/10.1586/ern.12.43

Deguchi, Y., Hayashi, H., Fujii, S., Naito, T., Yokoyama, Y., Yamada, S., & Kimura, R. (2000). Improved brain delivery of a nonsteroidal anti-inflammatory drug with a synthetic glyceride ester: a preliminary attempt at a CNS drug delivery system for the therapy of Alzheimer's disease. *Journal of Drug Targeting*, 8(6), 371-381. https://doi.org/10.3109/10611860008997913

Fernández, M., Barcia, E., Fernández-Carballido, A., Garcia, L., Slowing, K., & Negro, S. (2012). Controlled release of rasagiline mesylate promotes neuroprotection in a rotenone-induced advanced model of Parkinson's disease. *International Journal of Pharmaceutics*, 438(1-2), 266-278. https://doi.org/10.1016/j.ijpharm.2012.09.024

Giacobini, E., & Gold, G. (2013). Alzheimer disease therapy-moving from amyloid-β to tau. *Nature Reviews Neurology*, 9(12), 677-686. https://doi.org/10.1038/nrneurol.2013.223

Goldstein, D. S., Holmes, C., Sewell, L. (2011). Effects of carbidopa and entacapone on the metabolic fate of the norepinephrine prodrug L-DOPS. *The Journal of Clinical Pharmacology*, 51(1), 66-74. https://doi.org/10.1177/0091270010363476

Gonzalez, F. (2009). Diphenhydramine may be useful as a palliative treatment for patients dying with Parkinson's disease and tremors: a case report and discussion. *American Journal of Hospice & Palliative Medicine*, 26(6), 474-475. 10.1177/1049909109338937

Han, H. K., & Amidon, G. L. (2000). Targeted prodrug design to optimize drug delivery. *Aaps Pharmsci*, (1), 48-58. https://doi.org/10.1208/ps020106

Hey, J. A., Jeremy, Y. Y., Versavel, M., Abushakra, S., Kocis, P., Power, A., Kaplan, P. L., Amedio, J., & Tolar, M. (2018). Clinical pharmacokinetics and safety of ALZ-801, a novel prodrug of tramiprosate in development for the treatment of Alzheimer's disease. *Clinical Pharmacokinetics*, 57(3), 315-333. https://doi.org/10.1007/s40262-017-0608-3

Jellinker, K. A. (2003). General aspects of neurodegeneration. *Journal of Neural Transmission*, 65, 101-144. https://doi.org/10.1007/978-3-7091-0643-3_7

Jellinger, K. A. (2010). Basic mechanisms of neurodegeneration: a critical update. *Journal of Cellular and Molecular Medicine*, 14(3), 457-487. https://doi.org/10.1111/j.1582-4934.2010.01010.x

Kianirad, Y., & Simuni, T. (2016). Novel approaches to optimization of levodopa therapy for Parkinson's disease. *Current Neurology and Neuroscience Reports*, 16. https://doi.org/10.1007/s11910-016-0635-8

Lardenoije, R., van den Hove, D. L. A., Havermans, M., van Casteren, A., Le, K. X., & Palmour, R. (2018). Age-related epigenetic changes in hippocampal subregions of four animal models of Alzheimer's disease. *Molecular and Cellular Neuroscience*, 86, 1-15. https://doi.org/10.1016/j.mcn.2017.11.002

Lima, L., Pereira, S., Junior, R., Santos, F., Nascimento, A., Feitosa, C. (2018). A brief review on the

neuroprotective mechanism of vitexin. *BioMed Research International*, 2018, 1-8. https://doi.org/10.1155/2018/4785089

Mannila, A., Rautio, J., Lehtonen, M., Järvinen, T., & Savolainen, J. (2005). Inefficient central nervous system delivery limits the use of ibuprofen in neurodegenerative diseases. *European journal of pharmaceutical sciences*, 24(1), 101-105. https://doi.org/10.1016/j.ejps.2004.10.004

Marsden, C. D., Parkes, J. D., & Rees, J. E. (1973). A year's comparison of treatment of patients with Parkinson's disease with levodopa combined with carbidopa versus treatment with levodopa alone. Lancet, 302(7844), 1459-1462. https://doi.org/10.1016/S0140-6736(73)92729-3

McBride, J. L., Behrstock, S. P., Chen, E. Y., Jakel, R. J., Siegel, I., Svendsen, C. N., & Kordower, J. H. (2004). Human neural stem cell transplants improve motor function in a rat model of Huntington's disease. *Journal of Comparative Neurology*, 475(2), 211-219. https://doi.org/10.1002/cne.20176

Melo, A., Monteiro, L., Lima, R. M. F., de Oliveira, D. M., de Cerqueira, M. D., & El-Bachá, R. S. (2011). Oxidative stress in neurodegenerative diseases: mechanism and therapeutic perspectives. *Oxidative Medicine and Cellular Longevity*, 2011, 1-14. https://doi.org/10.1155/2011/467180

Müller ,T. (2015). Catechol-O-methyltransferase inhibitors in Parkinson's disease. *Drugs*, 75, 157-174. https://doi.org/10.1007/s40265-014-0343-0

Müller, M. L. T. M., & Bohnen, N. I. (2013). Cholinergic dysfunction in Parkinson's disease. *Current Neurology and Neuroscience Reports*, 13(9), 377. https://doi.org/10.1007/s11910-013-0377-9

Nazarenko, I. V., MSh, Z., Volkov, A. V., Kamenskiĭ, A. A., & RKh, Z. (1999). Functional-morphologic evaluation of the effect of the regulatory peptide kyotorphin on the status of the CNS in the post-resuscitation period. *Patologicheskaia Fiziologiia i Eksperimental'naia Terapiia*, 1(2), 31-33. https://europepmc.org/article/med/10379182

Novakova, I., Subileau, E. A., Toegel, S., Gruber, D., Lachmann, B., Urban, E., Chesne, C., Noe, C. R., & Neuhaus, W. (2014). Transport rankings of non-steroidal antiinflammatory drugs across blood-brain barrier in vitro models. *PloS One*, 9(1), e86806. https://doi.org/10.1371/journal.pone.0086806

Pasinetti, G. M., & Aisen, P. S. (1998). Cyclooxygenase-2 expression is increased in frontal cortex of Alzheimer's disease brain. *Neuroscience*, 87(2), 319-324. https://doi.org/10.1016/S0306-4522(98)00218-8

Pignatello, R., Pantò, V., Salmaso, S., Bersani, S., Pistarà, V., & Keep, V. (2008). Flurbiprofen derivatives in Alzheimer's disease: Synthesis, pharmacokinetic and biological assessment of lipoamino acid prodrugs. *Bioconjugate Chemistry*, 19(1), 349-357. https://doi.org/10.1021/bc700312y

Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., Schrag, A-E., & Lang, A. E. (2017). Parkinson disease. Nature Reviews Disease Primers, 3. https://doi.org/10.1038/nrdp.2017.13

Rautio, J., Kumpulainen, H., Heimbach, T., Oliyai, R., Oh, D., Järvinen, T., & Savolainen, J. (2008). Prodrugs: design and clinical applications. *Nature reviews Drug discovery*, 7(3), 255-70. https://doi.org/10.1038/nrd2468

Rinne, U., & Mölsä, P. (1979). Levodopa with benserazide or carbidopa in Parkinson disease. *Neurology*, 29(12), 1584-1589. https://doi.org/10.1212/WNL.29.12.1584

Roy, R., Deb, J., Jana, S. S., & Dastidar, P. (2014). Peptide conjugates of a nonsteroidal anti-inflammatory drug as supramolecular gelators: Synthesis, characterization, and biological studies. *Chemistry An Asian Journal*, 9(11), 3196-3206. https://doi.org/10.1002/asia.201402672

Santos, S. S., Santos, S. M., Pinto, A. R., Ramu, V. G., Heras, M., Bardaji, E., Tavares, I., & Castanho, M. A. (2016). Amidated and ibuprofen-conjugated kyotorphins promote neuronal rescue and memory recovery in cerebral hypoperfusion dementia model. *Frontiers in aging neuroscience*, 8. https://doi.org/10.3389/fnagi.2016.00001

Savica, R., Grossardt, B. R., Bower, J. H. (2013). Incidence and pathology of synucleinopathies and tauopathies related to Parkinsonism. *JAMA Neurology*, 70(7), 859-866. https://jamanetwork.com/journals/jamaneurology/article-abstract/1688412

Saydoff, J. A., Liu, L. S., Garcia, R. A., Hu, Z., Li, D., & von Borstel, R. W. (2003). Oral uridine pro-drug PN401 decreases neurodegeneration, behavioral impairment, weight loss and mortality in the 3-nitropropionic acid mitochondrial toxin model of Huntington's disease. *Brain research*, 994(1), 44-54. https://doi.org/10.1016/j.brainres.2003.09.049

Sestito, S., Daniele, S., Pietrobono, D., Citi, V., Bellusci, L., Chiellini, G., Calderone, V., Martini, C., & Rapposelli, S. (2019). Memantine prodrug as a new agent for Alzheimer's Disease. *Scientific Reports*, 9(1), 1-1. https://doi.org/10.1038/s41598-019-40925-8

Sinkula, A. A., & Yalkowsky, S. H. (1975). Rationale for design of biologically reversible drug derivatives: prodrugs. *Journal of pharmaceutical sciences*, 64(2), 181-210. https://doi.org/10.1002/jps.2600640203

Tampio, J., Huttunen, J., Montaser, A., & Huttunen, K. M. (2020). Targeting of perforin inhibitor into the brain parenchyma via a prodrug approach can decrease oxidative stress and neuroinflammation and improve cell survival. *Molecular Neurobiology*, 57(11), 4563-4577. https://doi.org/10.1007/s12035-020-02045-7

Tutone, M., Chinnici, A., Almerico, A. M., Perricone, U., Sutera, F. M., & De Caro, V. (2016). Design, synthesis and preliminary evaluation of dopamine-amino acid conjugates as potential D1 dopaminergic modulators. *European Journal of Medicinal Chemistry*, 124, 435-444. https://doi.org/10.1016/j.ejmech.2016.08.051

Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T. D., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *International Journal of Biochemistry and Cell Biology*, 39(1), 44-84. https://doi.org/10.1016/j.biocel.2006.07.001

Xilouri, M., Brekk, O. R., & Stefanis, L. (2012). Alpha-synuclein and protein degradation systems: a reciprocal relationship. *Molecular Neurobiology*, 47, 537-551. https://doi.org/10.1007/s12035-012-8341-2

Zhang, Q., Liang, Z., Chen, L. Y., Sun, X., Gong, T., & Zhang Z. R. (2012). Novel brain targeting prodrugs of naproxen based on dimethylamino group with various linkages. *Arzneimittelforschung Drug Research*, 62(6), 261-266. 10.1055/s-0032-1306273

Zhou, T., Hider, R. C., Jenner, P., Campbell, B., Hobbs, C. J., Rose, S., Jairaj, M., Tayarani-Binazir, K. A., & Syme, A. (2010). Design, synthesis and biological evaluation of L-dopa amide derivatives as potential prodrugs for the treatment of Parkinson's disease. *Eurpean Journal of Medicinal Chemistry*, 45(9), 4035-4042. https://doi.org/10.1016/j.ejmech.2010.05.062