Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

New facets of neuroprotective effects of nonsteroidal anti-inflammatory drugs: A comprehensive review

ApinaK*, Muhammed Khais, AnusreeV, Thasleena V.P., Parvathy S.L., Nija B., Arun Rasheed

Department of Pharmaceutical Chemistry, Al Shifa College of Pharmacy, Poonthavanam, Perinthalmanna, Malappuram, Kerala

ARTICLE HISTORY

Received: 12.03.2020

Accepted: 22.06.2020

Available online: 30.06.2020

Keywords:

Microglia, PPARs, Blood brain barrier, Drug delivery systems.

***Corresponding author:**

Phone : +91-9496742242
Email : apinakelothsn@gmail.com

ABSTRACT

Neurodegeneration is defined “as the progressive loss of structure or function of neurons, including death of neurons". These include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). Neurodegenerative disorders are incurable with the medication that normally we used. The main drawback of this may be due to the low permeability of drug to blood brain barrier. The blood brain barrier act as a barrier which block the transport of neurotoxins and chemicals.Some of the researchers postulated that long term use of NSAIDs reduces the risk of developing neurodegenerative disorders. NSAIDs are mainly used for the treatment of pain, inflammation, osteoarthritis, and rheumatoid arthritis. But those NSAIDs may produce side effects such as gastric irritation, bleeding, stomach ulcer etc. In order to overcome those side effects, 'prodrug' approach could be done. In this paper explore NSAIDs used for neurodegenerative disorders by a prodrug approach and also reveals different carriers/ linkers used for the production of prodrugs.

INTRODUCTION

Now a days the development of neurodegenerative disorders reach at a peak level due to life style changes and also aging in population [1]. Neurodegeneration is the progressive loss of structure or function of neurons including death of neurons. Neurons are the building blocks of brain and spinal cord. Inflammation is a major risk factor for the development of neurodegenerative disorders [2]. Inflammation increases both systemically and in central nervous system during normal aging process. One of the most important facts with neurodegenerative disorders is that they are incurable. There are no drug treatment that can cure the Alzheimer's disease and Parkinson's disease completely, they only reduces the further progression of disease. Alzhimer's disease is characterized by the deposition of beta-amyloid plaques in hippocampus and cerebral cortical region. Alzheimer's is an age dependant disorder and it destroys patient's memory and cognition in geriatric population [3, 4]. Parkinson's disease is a second most neurodegenerative disorder that is characterized by tremor, rigidity and bradykinesia [5]. More number of synthetic as well as naturaldrugs are available for treating neurodegenerative disorders, but they have limited therapeutic efficacy because due to their low bioavailability, high toxicities on liver and kidney. In order to overcome these drawbacks prodrug based approach can also be used. Prodrugs are more stable and better than the corresponding parent drugs.In the present situation several non toxic conjugates can be used for the development of prodrugs for the targeted drug delivery thus overcome the various barriers of the existing drugs[6,7,8].

ALZHEIMER'S DISEASE

Alzheimer's disease is the prominent neurodegenerative disorder seen in elderly peoples.One of the main feature of Alzheimer's disease is the accumulation/aggregation of βamyliod proteins(40-42 aminoacids) extracellular and neurofibriliary tangles intracellular in hippocampus region of the brain[9,10]. The plaques are also associated with pro-inflammatory mediators such as cytokines,IL-1∞, IL-1β, IL-6 and tumor necrosis factor (TNF-∞). Microtubule associated tau protein in AD brain are abnormally phosphorylated.Those tau protein causes breakdown of microtubule system that leads to neuronal dysfunction and degeneration.It is characterized by cognitive decline, neuronal inflammation and neuronal death. The death of neurons is also calledapoptosis or necroptosis [11,12,13,14,15].The neuron in the AD brain is represented in figure1.

PARKINSON'S DISEASE

Parkinson's disease is clinically characterized by movement

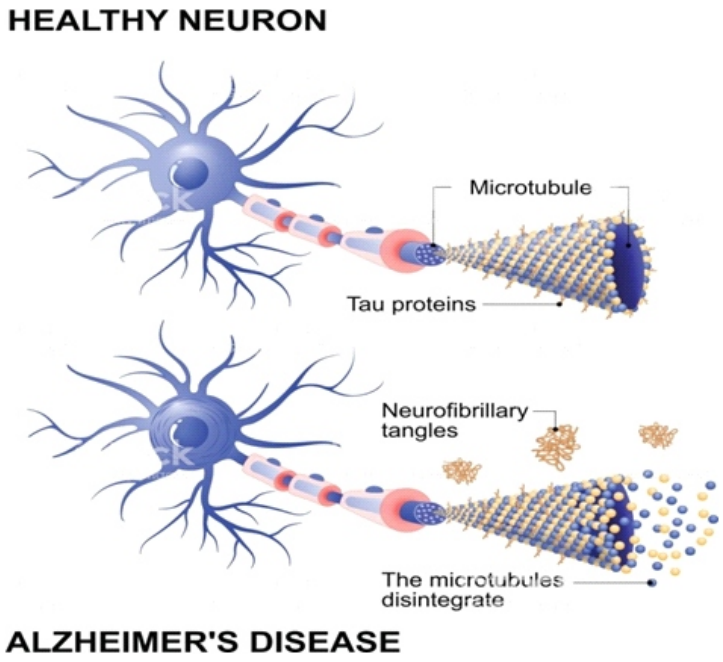

Fig. 1 : Alzheimer's disease brain

disorder, Including tremor, rigidity and bradykinesia [16]. Parkinson's disease is the second most chronic and progressive neurodegenerative diseases, mainly occurs due to the degeneration of dopaminergic neurons in substantianigra. Now a day's various pharmacological and non pharmacological treatments are available but they offer only symptomatic relief to the patients. Usually Levodopa is used for the treatment of PD acting as a dopamine precursor and it has an ability to decline various motor symptoms of PD. But long term use of levodopa produces undesirable side effects to patients [5, 17, 18]. Recent studies revealed that pathogenesisof parakinson's disease include neuro-inflammation and microglial activation, due to this fact some of the NSAIDs are used for the treatment of PD.Although treatments with NSAIDs doesnot offer a complete cure of PD, but its long term use reduces the risk of developing PD[19, 20].

BIOLOGICAL MECHANISM

The mechanisms of neurodegenerative disorders are unclear because of that effective treatments protocols are not available. Many of the hypothesesare developed to explain the mechanisms behind Neurodegeneration.

Oxidative stress

Oxidative stress and generation of reactive oxygen species (ROS) are considered as the major pathogenesis of Neurodegeneration. Oxidative stress is generated byimbalance between ROS generation and antioxidant defenses. The reactive oxygen species are produced by both endogenous and exogenous process. Endogenoussources includelipoxygenase, angiotensin and nicotinamide adenine dinucleotide phosphate oxidase (NADPH). Exogenous sources are air, tobacco, transition metals, alcohol and drugs such as tacrolimus, gentamycin etc. By using antioxidants the oxidative stress may reduced. Both natural and synthetic anti oxidants are available; they have ability to treat neurodegenerative diseases caused due to oxidative stress. Endogenousanti oxidants are enzymes such as SOD, catalase, glutathione peroxidase. Ascorbic acid, vitamin E, superoxide radical anion are major exogenousantioxidants [21, 22].

Neuroinflammation

Inflammation is a physiological immune response against infection, trauma and other diseases. Neuroinflammation is one of the principle pathogenesis in Neurodegeneration [23]. The initiatition of neuroinflammation shows neuronal dysfunction. Glial cells composed of astryocytes and microglia mediate inflammation in brain. In AD neuroinflammation is considered as the cause of dementia. Different types of inflammatory mediators are seen in the senile plaques in the brain of AD patients. In PD neuroinflammation produce an effect on dopaminergic neurons and also cause death of other brain cells. During the process of inflammation several inflammatory and pro inflammatory mediators are secreted. Pro inflammatory mediators are cytokines, chemokines, bradykinin and also transcription factors (TNF-α)[24, 25].

Mitochondrial dysfunction

Mitochondria are one of the vital dynamic cellular organelles, performs many functions especially for the maintenance of cellular energy homeostasis. Some of the studies suggest that any deterioration in structure and function of mitochondria gradually leads to impairment of cognitive function and also neuronal death. Mitochondrial dysfunction is mainly due to impairment of electron transport chain, damage of mitochondrial DNA and impairment in calcium buffering system [26]. The main cause of parkinsonism is the production of mitochondrial toxin such as 1-methyl-4-pheny l-1,2,3,6-tetrahydropyridine (MPTP), they undergo metabolism to form MPP^{+}. Dopaminergic neurons taken up these metabolites and inhibit the electron transport chain that may also lead to neuronal death.

BLOOD BRAIN BARRIER (BBB)

Blood brain barrier comprises of highly specialized endothelial cell layers, which separates the interstitial fluid from blood. Endothelial cells are joined together by tight junctions, are

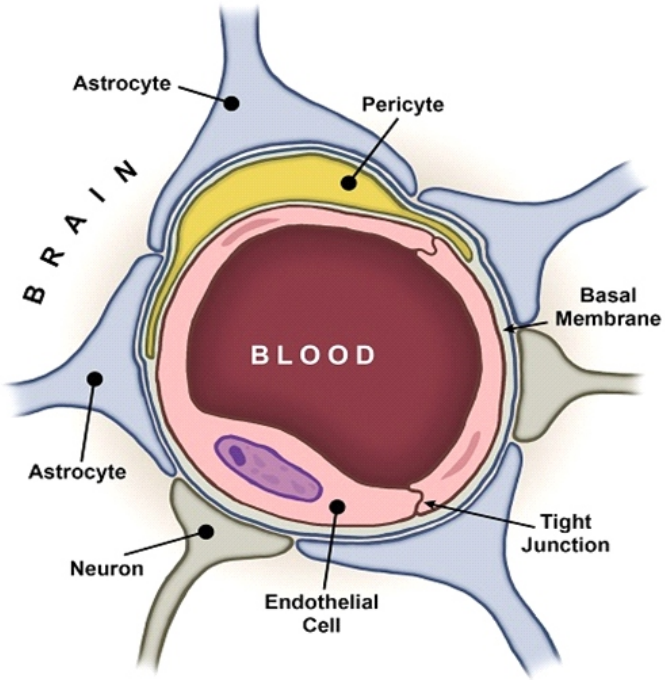

Fig. 2 : Blood brain barrier

more complex as compared to that of peripheral tissue endothelium. Tight junction prevents para cellular transport. Tightness of junctions is determined by measuring the level of transendothelial electrical resistance (TEER). The tight junction consists, two types of proteins such as membrane proteins as well as cytoplasmic proteins. Occludin, claudins and junctional adhesion molecules are major membrane proteins. Due to its unique properties, BBB limits the passage of some potential CNS drugs and also prevents the entry of neurotoxic substances such as proteins, xenobiotics (from the diet, toxins, drugs, pollutants),endogenous metabolitesetc[27,28,29].BBB act as a physical, transport, immunological and metabolic barrier. Physical barriers prevent paracellular transport and metabolic barrier prevent trans-cellular transport. Examples of intracellular and extracellular metabolizing enzymes includes monoamine oxidase, peptidases, cytochrome p-450 which convert convert the substrates into less toxic compounds and increases their permeability across BBB. Whenever the integrity of BBB losses inflammatory mediators such as cytokines and immune cells may enter into CNS, which activate glial cells and produce secondary inflammation as a result BBB damage occurs [30,31,32]. BBB has an ability to protect the cells from inflammation, injury and diseases. BBB permeates the transport of lipid soluble substances through diffusion but limits the permeability of highly polar compounds. In order to improve the passage across BBB saturable and non- saturable transport systems are developed. BBB plays an important role in the regulation of ions and providing ionic components for optimal neuronal signaling function [33,34,35,36,37,38,39]. The main function of BBB is to maintain homeostasis and it is represented in the figure 2.

Transport mechanisms

1. Transmembrane diffusion

Drugs that are used for treating neurodegenerative disorders cross the blood brain barrier by transmembrane diffusion.Low molecular weight and highly lipid soluble substances easily undergo transmembrane diffusion [40].

2. Carrier mediated transport

Different types of carriers are available to transport drugs into CNS. These carriers deliver both polar and non polar substances. Amino acids, peptides, vitamins, nucleoside, vitamin and glucose transporters are principle examples of carriers. One of the best example for carrier mediated transport is the passage of levodopa across BBB by using amino acids as carrier, due to fact that dopamine are unable to cross BBB[41,42].

Glucose transporters [GLUT]

One of the principle energy source of most of the mammalian cells, particularly in the brain is glucose or in other words sugars. Glucose and other sugars have the ability to cross blood brain barrier easily by utilizing glucose transporter proteins. The glucose transporters exist within the CNS as seven isoforms particularly GLUT1-7, among these GLUT1 and GLUT3 are major isoforms that transport the glucose into the cells by sodium independent transport mechanisms. Other carrier mediated transporters are given below [43].

- Large neutral amino acid transporter 1 (LAT1)
- Cationic amino acid transporter 1 (CAT1)
- Monocarboxylic acid transporter 1 (MCT 1)
- Concentrative nucleoside transporter 2 (CNT 2)

3. Receptor mediated transport

The mechanism is mainly used for the passage of larger peptides and proteins by endocytosis. Different types of receptors are used for transport across BBB. Transferrin receptors, insulin receptors, lipoprotein receptors, scavenging receptors and folate receptors are some of the examples [44].

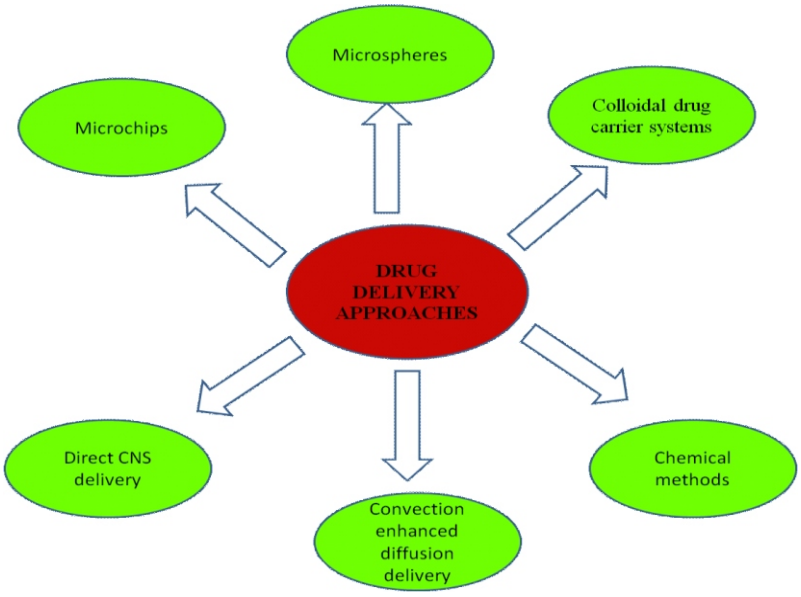

Fig. 3 : Drug delivery approaches

STRATEGIES TO DELIVER DRUGS INTO BRAIN

In order to improve the BBB permeability different strategies are available including viral and non viral vectors. Viral vectors are mainly used for the delivery of genes to patients with neurodegenerative disorders or other neurological disorders. Examples of viral vectors are adeno virus, adeno-associated virus, herpes simplex virus and lenti virus. But the viral vectors have limited application due to its high cost and difficulties in preparation. Normally viruses cannot cross blood brain barrier passively but they have ability to transfect the gene into the specific target cells. One of the major advantages of viral vectors is that high gene transfection efficiency.

In non-viral vectors includes the introduction of nanoparticle formulations. Due to its smaller or nano size (< 200nm) they easily cross blood brain barrier and also has the ability to release drugs in a controlled manner. The size of nanoparticles depends on nature and type of target tissue.In neuroinflammatory conditions there is a chance of increase the expression of transferrin and insulin receptors. Due to this fact transferrin and insulin receptors act as a target for nanoparticles [45].Different drug delivery approaches are summarized in figure 3.

PPAR□

Peroxisome proliferator-activated receptor (PPAR) is nuclear receptors, expressed in various tissues. They are mainly of three types such as PPAR∞, PPAR□, PPAR□. PPARs involved mainly in lipid metabolism and that may also play an important role in the control of inflammation. PPARs plays an major role in down regulation of proteosomal dysfunction, mitochondrial dysfunction and also oxidative stress that is why they serve as a promising target for various neurodegenerative disorders[46]. Several studies suggested that chronic usage of PPAR□ activating NSAIDs reduces the progression of neurodegenerative disorders. Some of the NSAIDs such as indomethacin, fenoprofen, and ibuprofen may activate PPAR∞ and PPAR.ɣVarious NSAIDs as well as other PPAR□ agonists (Thiazolidinedione class of drugs, natural ligand prostaglandin J2) expresses similar inhibition pattern on the inflammatory cytokines such as IL-6 and TNF∞ in microglia and astrocytes, which are responsible for neurotoxicity and astrocyte activation. Epidemiological studies suggest that PPAR□ may provide a promising therapeutic approach to AD patients by improving learning and memory [47]. In the case of PD PPAR□ protects cell bodies of dopaminergic neurons in substantianigra.

MICROGLIA

Microglias are the major immune cells present in brain originating from mesodermally derived macrophages that may become permanently resident in brain. They exist in both activated and resting state.Microglia is activated by infectious agents such as bacteria, viruses and lipopolysaccharides. In the activated state they produce large amounts of superoxidesand other potential neurotoxinsinclude tumor necrosis factor (Proinflammatory cytokines), reactive nitrogen species, proteases, excitatory amino acids and eicosanoids. In microglia, phagocytosis occurs and partly degrades the amyloid fibrils. Microglia considered as the principle target for the anti inflammatory action of NSAIDs, is a major source of prostaglandins[48,49].

ASTROCYTES

Astrocytes areinnate immune cells present in CNS. They have functions such as regulation of protein signaling, maintenance and formation of blood brain barrier complex structure, synaptogenesis and also regulate homeostasis. Some of the studies suggest that astrocytes have a role on cognitive impairment and neuronal loss by high reactivity on some conditions such as excitotoxicity, injury and infection. Astrocyte reactivity is defined as the loss of astrocyte morphology as well as their function, is a hallmark of both aging and age related disorders. Astrocytes plays a key role in mitochondrial dysfunction, neuronal death and other process associated with neurodegenerative disorders. Recent studies suggest that astrocyte become a novel target for treatment of several CNS related diseases [50,51].

NSAIDs AS NEUROPROTECTIVE AGENTS

Aspirin

In older days aspirin is used as a anti platelet agent, because they inhibit platelet aggregation through the inhibition of COX-1 enzyme. Later some studies revealed that Aspirin inhibit both COX-1 and COX-2 enzyme. COX-2 inhibition produces its anti-inflammatory activity. Aspirin has the ability to reduce oxidative stress and protect against oxidative damage and also dampens ROS mediated signaling[52].The structure of aspirin is shown in figure 4.

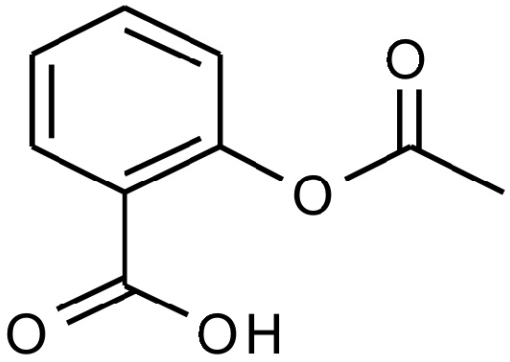

Fig. 4 : Aspirin

Ibuprofen

Ibuprofen is one of the most commonly used NSAID for inflammation, dental pain,menstrualcramps,muscle aches and also arthritis and the structure is given in figure 5. Ibuprofen is a propionic acid derivative; it has mechanism of action on both COX-1 and COX-2 enzyme. Ibuprofen exist as two enantiomeric form that (+) and (-) ibuprofen, among these (+) ibuprofen/dexibuprofen is the principle enantiomer used for neurodegenerative disorders. Oxidative stress is one of the major risk factor responsible for the Neurodegeneration in Alzheimer's disease. For treating neurodegenerative disorders ibuprofen conjugated with an antioxidant such as (R)-∞- Lipoic acid. The synthesized compounds reduce β-amyloid peptide production [53].

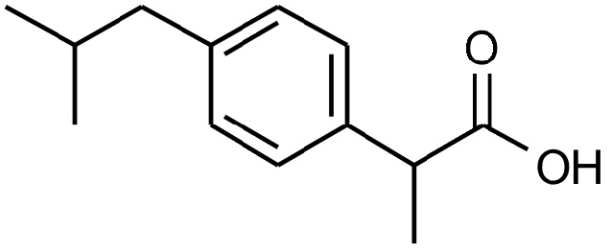

Fig. 5 : Ibuprofen

Mefenamic acid

Mefenamic acid is an anthranilic acid derivative belongs to a class of non selective COX inhibitors and the structure is given in figure 6. Mefenamic acid mainly used for treating inflammation, pain, arthritic conditions etc. Sustained use of mefenamic acid exhibits neuroprotective activity, they attenuatesneuro toxicities. Mefenamic acid has an ability to decline the production of nitric oxide and free radicals. Mefenamic acid improves learning and memory by reducing levels of Aβ(1-42) amino acid[54].

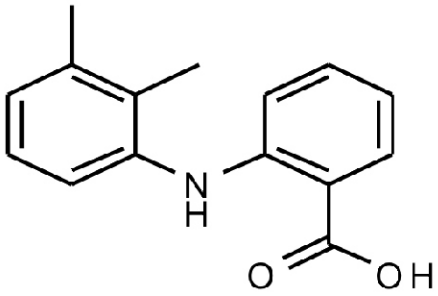

Fig. 6 : Mefenamic acid

Indomethacin

Indomethacin is a non selective COX inhibitor and the structure is given in figure 7. It is effective for the treatment of Alzheimer's disease due to the fact that, effect on pro inflammatory cytokines as well as tumor necrosis factor. Indomethacin act by preventing the neuronal cell damage and neuronal death in various neurodegenerative diseases associated with DNA fragmentation. Indomethacin improves the sensor motor coordination and enhances short term memory in elderly population [55].

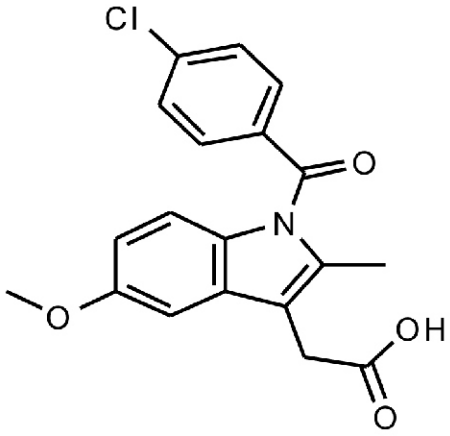

Fig. 7 : Indomethacin

Tolfenamic acid

Tolfenamic acid belongs to fenamate class of drugs. It has ability to attenuate the cognitive deficits. Improve memory and spatial learning by reducing the Aβ pathology.Tolfenamic acid decreases the levels of amyloid precursor protein (APP) and also amyloid beta [56] and the structure is shown in figure 8.

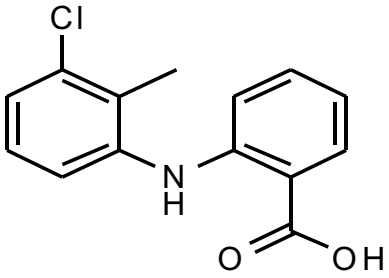

Fig. 8 : Tolfenamic acid

Flurbiprofen

Flurbiprofen is one of the important drugs in propionic acid derivative class and it exerts a multiple actions on Alzheimer's disease pathology [57]. The structure of flurbiprofen is given in figure 9.

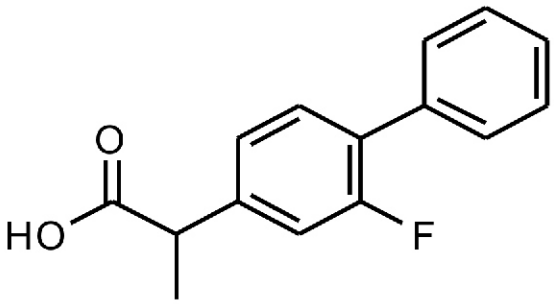

Fig. 9 : Flurbiprofen

Sulindac

Sulindac inhibits the two COX isoforms such as COX-1 and COX-2 enzymes and given in figure 10.Sulindac is one of the principle example of prodrug approach, they metabolized into sulfide and sulfone form. Among these two metabolites sulfide form possess COX inhibitory activity, the other sulfone form has no activity [58].

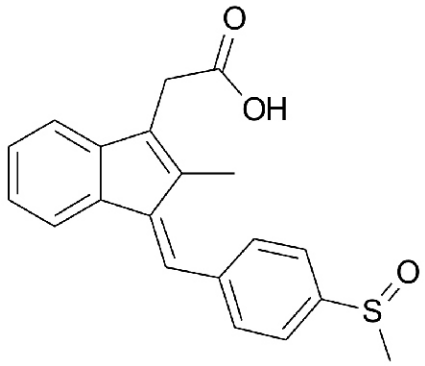

Fig. 10 : Sulindac

Table 1 : Examples of NSAIDs, conjugates and their activity.

Sl.No	Drug	Conjugate	Activity	Reference
1	Ibuprofen	L-Proline	Nootropic action	I.C.Siskou. et al.,2007
		R-8 Lipoic acid	Reduce β amyloid production	A. Di Stefano et al., 2010
2	Tolfenamic acid	Specificity protein 1	Attenuate the cognitive deficits.	Subacia. et al, 2012
3	Mefenamic acid	D-Serine	Regulation of oxidative stress, apoptosis and inflammation	GulizArmagan. et al.,2012
4	Tolmetin	Quinolic acid	Anti oxidant activity Neuroprotective activity	AmichandDairam et al., 2006
5	Sulindac	Quinolic acid	Anti oxidant activity	AmichandDairam et al, 2006
6	Flurbiprofen	Nitric oxide releasing derivatives, HCT1026,NCX2216	Inhibit activation of microglia.	Laura Gasparini et. al.,2005
		Polylactide nanoparticles	Facilitate drug delivery to the brain.	Sabrina Meister et al.,2013
		Dendrimer based carriers	Facilitate brain delivery and targeting.	ShafqK. Al-azzawi et. al, 2017
		Lipoaminoacids (LAA)	Increase the blood brain barrier permeability.	Rosario Pignatello et. al.,2007
7	Naproxen	Ascorbic acid, Glucose	Neuroprotective effect	Wangetet. al., 2017
8	Ketoprofen	Anti oxidants	Neuroprotective effect Anti oxidant activity Anti inflammation	ShikhaSchajpal et. al., 2018

CONCLUSION

The present review concluded that the NSAIDs having the property to reduce the initiation and progression of degenerative conditions in the brain.The NSAIDs have wide range of therapeutic actions such as anti-inflammatory, analgesic, anti pyretic, rheumatoid arthritis etc. Several mechanisms were put forward to explain the development of neurodegeneration, that include neuro-inflammation,oxidative stress, mitochondrial dysfunction, accumulation of proteins in neurons, damage in blood brain barrier etc. NSAIDs may elicit a significant role to reduce the mechanisms seen in Neurodegeneration but the distribution of NSAIDs in brain is limited due to the hydrophilic nature. Various targeted drug delivery strategies can be used to overcome the limited brain distribution of NSAIDs and among this prodrug based drug design is one of the effective methods. In prodrug approach, different types of natural and synthetic conjugates can be used and that results the modified drug having the improved lipophilicity, bioavailability, transport properties, other physical, chemical and pharmacological activities as well as reduction in the toxicity profile. The NSAIDs generally act through the inhibition of both COX enzymes such as COX-1 and COX-2 and decreases the prostaglandin synthesis and studies revealed that also some other properties such as reduction in the superoxide radicals, decreases nitric oxide synthase, decrease pro inflammatory cytokines. Review showed that the use of NSAIDs provide the protective effect in the brain against neurodegenerative conditions and different targeted drug delivery methods can be adopted for the better brain distribution of NSAIDs thus nootropic effect.

REFERENCES

1. TomrisOzben et al., Neuro-inflammation and Anti-inflammatory treatment options for Alzheimer's disease, 2019,(72),87-89
2. Kushalkumar et al., Recent advances in the neurobiology and neuropharmacology of Alzheimer's disease, 2018, (98), 297-307
3. Jefferson w. Kinney et al., Inflammation as a central mechanism in Alzheimer's disease.2018,1-16
4. LlariaLiguori et al., Oxidative stress, aging and diseases, 2018, (13), 757-772
5. Li Ren et al., Nonsteroidal anti inflammatory drugs use and risk of parkinson's disease,2018
6. Murat Terzi et al., The use of non-steroidal anti-inflammatory drugs in neurological diseases.2017,
7. Monica Molteni et al., Neurodegenerative diseases: The immunological perspective.2017,(313),109-115
8. Jaya PreethiPeesa et al., A perspective review on role of novel NSAID prodrugs in the management of acute inflammation, 2016,5(5), 364-381
9. Waisudin et al., Encapsulation of NSAIDs for inflammation management : Overview, progress, challenges, and prospects,2016(16)
10. Anil Kumar et al., A review on Alzheimer's disease pathophysiology and its management: an update, 2015,(67),195-223
11. MahmoodRasool et al., Recent updates in the treatment of neurodegenerative disorders using natural compounds, 2014,
12. JafarDoost Mohammad Pour et al.,Non selective NSAIDs improve the amyloid β mediated suppression of memory and synaptic plasticity, 2015,
13. Sandra Rocha et al., Targeted drug delivery across the blood brain barrier in Alzheimer's disease,2013,(37),6635-6646
14. EironCudaback et al., Therapeutic implications of the prostaglandin pathway in Alzheimer's disease.2013,
15. Sharlene Cote et al., Non steroidalanti inflammatory drug use and the risk of cognitive impairment and Alzheimer's disease.2012,(8), 219-226
16. Yang Hong-Qi et al., Current advances in the treatment of Alzheimer's disease: focused on considerations targeting Aβ and tau,2012
17. Xiaoting Sun et al., Review of drugs for Alzheimer's disease, 2012, (6), 285-290
18. Richard Gordon et al., Neuroinflammation as a therapeutic target in neurodegenerative diseases, 2017
19. PieraSozio et al., Designing prodrugs for the treatment of Parkinson's disease, 2012,7(5),385-406
20. Neha Singh et al., Advances in the treatment of parkinson's disease, 2007 (81),29-44
21. Ennio Esposito et al., Non steroidal anti-inflammatory drugs in parkinson's disease. 2007 (205), 295-312
22. AiltonMelo et al.,Oxidative stress in neurodegenerative diseases: Mechanisms and therapeutic perspectives, 2011,1-14
23. Jintang Wang et al., Connection between systemic inflammation and neuroinflammation underlies neuroprotective mechanism of several phytochemicals in neurodegenerative diseases, 2018,1-16
24. Estella A. Newcombe et al., Inflammation: the link between comorbidities, genetics, and Alzheimer's disease, 2018, (15),276
25. Swati agarwal et al., Peroxisome proliferator activated receptors as therapeutic target in neurodegenerative disorders, 2016,
26. Magdalena Sastre et al., NSAIDs : how they work and their prospects as therapeutics in Alzheimer's disease, 2010
27. Marta A Malkiewicz et al., Blood brain barrier permeability and physical exercise ,2019
28. Docent PekkaJarho, Central nervous system permeation of Ibuprofen, Ketoprofen and Indomethacin, 2019
29. Isra' Zeiadeh et al ., Strategies for enhancing the permeation of CNS-active drugs through blood brain barrier, 2018,
30. Shafq K. Al azzawi, Improving flurbiprofen brain permeability and targeting in Alzheimer's disease by using a novel dendronised Apo-E derived peptide carrier system,2017
31. Kathryn P. MacPherson et al., Neuroinflammation in Age related neurodegenerative disorders ,2018
32. Richard Daneman et al., The blood brain barrier , 2015

33. Siddhartha Dalvi et al., The blood brain barrier regulation of fatty acid and drug transport,2014
34. Sandra Rocha, Targeted drug delivery across the blood brain barrier in Alzheimer's disease, 2013,19(37),6635-6646
35. I.D .Serrano et al., A Focus on glucose mediated drug delivery to the central nervous system, 2012,12, 301-312
36. Sandipan Roy, Strategic drug delivery targeted to the brain : A Review,2012,3(1),76-92
37. Courtney D et al., Analytical and biological methods for probing the blood brain barrier, 2012
38. JarkkoRautio et al., Prodrug approaches for CNS delivery, 2008,(10)
39. Barbara Pavan et al., Progress in drug delivery to the central nervous system by the prodrug approach, 2008,13,1035-1065
40. William A Banks, Characterestics of compounds that cross blood brain barrier,2009
41. Mayur M. Patel et al., Crossing the blood brain barrier : Recent advances in drug delivery to the brain, 2017,(31), 109-133
42. Courtney D. Kuhnlinesloan et al., Analytical and biological methods for probing the blood brain barrier ,2012,(5),505-531
43. Richard Daneman et al., The blood brain barrier,2015,
44. XiaoweiDong , Current strategies for brain drug delivery,2018,(6),1481-1493
45. Luca Anna Bors et al., Overcoming the blood brain barrier. Challenges and tricks for CNS drug delivery, 2019,(87)
46. Swati Agarwal et al., Peroxisome proliferator-activated receptors (PPARs) as therapeutic target in neurodegenerative disorders, 2016,(16) ,
47. Paul S. Aisen,Development of anti inflammatory therapy for Alzheimer's disease, 2002(56) 421-427
48. Yaun Dong et al., Drug development for Alzheimer's disease: Microglia induced neuroinflammation as a target,2019,
49. Maria Antonietta Ajmone cat et al., Non steroidalanti inflammatory drugs and brain inflammation: Effect on microglial functions, 2010,(3), 1949-1964
50. Luisa Minghetti, Role of inflammation in neurodegenerative , 2005,(18),315-321
51. Hui-Ming Gao et al., Novel anti-inflammatory therapy for Parkinson's disease 2003,(24),
52. C. Cornelius et al., Aspirin, NSAIDs, Risk of dementia, and influence of the Apolipoprotein E Epsilon 4 allele in an elderly population,2004,(23),135-143
53. QimingYue et al., Dual targeting for brain-specific drug delivery: synthesis and biological evaluation,2018,25(1), 426-434
54. Ioanna C. Siskou et al., Design and study of some novel ibuprofen derivatives with potential nootropic and neuroprotective properties,2007, (15), 951-961
55. YanpingLi et al., Mechanism of brain targeting by dexibuprofenprodrugs modified with ethanolamine related structures,2015,(35),1985-1994
56. Zaman Ashraf et al., Synthesis, characterization and in vitro hydrolysis studies of ester and amide prodrugs of dexibuprofen, 2012,(21), 3361-3368
57. Gulizarmagan et al., Neuroprotection by mefenamic acid against D-serine: Involvement of oxidative stress, inflammation and apoptosis, 2012,46(6), 726-739
58. Yuyoungjoo et al., Mefenamic acid shows neuroprotective effects and improves cognitive impairment in invitro and invivo Alzheimer's disease models, 2005