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Review Article

REVIEW ON EVALUATING THE ROLE OF NSAIDS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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ABSTRACT

Recently, several studies have been reported that nonsteroidal anti-inflammatory drugs can fight against neurodegenerative disorders by various mechanisms. Currently, available therapies of neurodegenerative disorders (NDs) provide only symptomatic relief. This is the point at which we need an alternative that acts on the root cause of disease. Parkinson's disease and Alzheimer's disease are the two NDs concentrated here. Since the drug profile is already known, drug repurposing is a promising technique in research, thereby reducing the cost and period effectively. Epidemiological studies on various nonsteroidal anti-inflammatory drugs (NSAIDs) showed good results, but when it came to clinical studies the results are found to be poor. Hence, it can be concluded that NSAIDs provide its neuroprotective activity on its long-term use only, as the brain accessibility of this kind of drug is poor due to its lower lipophilicity.

Keywords: Nonsteroidal anti-inflammatory drug, Alzheimer's disease, Neurodegeneration, Neuroinflammation, COX-1 and COX-2, Aβ

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INTRODUCTION

Neuroprotection is referred to as approaches and correlated mechanisms that protect our central nervous system from neuronal injuries because of chronic or acute neurodegenerative disorders (NDs). The incidences of NDs are a result of deterioration and breakdown of neurons that finally leads to a cognitive and behavioral imbalance in patients.

The symptoms of NDs include memory loss, learning difficulties, motor coordination, and other functional losses. Hypertension, other infections, environmental and genetic factors are the reasons underlying the disease. Other than these reasons, aging assumes a significant part in the rate of illness. The pathology associated with NDs includes the aggregation of proteins, inflammation, oxidative stress [1], and loss of neurotransmitters [2, 3]. Since the available treatments like Rivastigmine, Galantamine, Donepezil, Memantine, Memantine combined with Tacrine, and Donepezil are coming under supportive therapy regulating the levels of neurotransmitters, there is a great need for a new derivative for the root cause of the disease [2, 4].

Recent studies on NSAIDs have been proven that they can extent neuronal inflammation associated with the pathophysiology of neurodegenerative disorders. Epidemiological as well as immunochemical studies, suggested that individuals on long term anti-inflammatory drug treatment will reduce the risk of occurrence of NDs in elderly persons [5].

Since NSAIDs are widely used over the counter medication and the drug profile is already well known, drug repurposing is a promising method for the treatment of NDs. For further clarification on this review, we are correlating published data regarding NSAIDs as well as Alzheimer's and Parkinson's disease.

Search criteria

This review included articles from 1990 to 2020 that were found in various electronic databases PubMed, Science Direct, Scopus, Web of Science, and Google Scholar by using the search words: neurodegenerative diseases, neuroprotection, antioxidant, Alzheimer's disease, Parkinson Disease, Amyotrophic Lateral Sclerosis, Prion Diseases, Huntington Disease, mechanism of neurodegenerative disorders, NSAIDs, various NSAIDs used for the treatment of Alzheimer's disease.

Neurodegenerative disorders

The major cause of the neurodegenerative disorder (ND) is neuronal cell death, particularly in the area of the CNS. Alzheimer's disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Lewy body dementia (LBD), amyotrophic lateral sclerosis (ALS), Spongiform encephalopathy (Prion disease), and Huntington's disease are such NDs [6]. Among these, Alzheimer's disease is the most prevalent one, followed by Parkinson's disease. NDs mainly affects the behavioral and cognitive functions of the patient. In all of these conditions, age plays a major role. Therefore, we can say that age is a risk factor for these types of diseases. The pathophysiology includes protein aggregation, inflammation, oxidative stress, and neurotoxicity [3, 7].

Alzheimer's disease (AD)

Alzheimer's is a cumulative degenerative malady with early signs of forgetting recent events or conversations [8]. Progressively, the patient develops serious memory loss and incapability to run day-to-day tasks. The available treatments for AD may only temporarily mask the symptoms and occasionally boost function and maintain independence for a time. Currently, no treatments offer a complete cure for this disease [4]. Difficulties from acute loss of brain function like dehydration, malnutrition, or infection are seen in the final stages of the disease, which will ultimately lead to death. It is believed that an association of genetic, lifestyle and environmental factors are the reasons behind AD. The precise reason for AD is still inconclusive, but a vital role is played by brain proteins that have lost their normal functioning, thereby disturbing neurons, and as a result, a series of toxic events occur. The symptoms will appear only after years when the damage occurs in the area that controls memory [9]. The loss of neurons extends predictably to other regions of the brain. The brain eventually gets shrunk in the late stages of the disease [3, 10].

Two proteins that play a major role in AD

Plaques: Plaques are dense insoluble leftover fragments of a larger protein called beta-amyloid, which is pruned from amyloid precursor protein (APP), having a toxic effect on other neurons and disturb cell to cell communication.

Tangles: Nutrients and other essential materials are transported by tau proteins and also act as internal support to neurons. In Alzheimer's disease, the transport system is disturbed by neurofibrillary tangles, which are formed as a result of structural changes and the organization of tau proteins [7, 11].

Parkinson disease (PD)

PD is yet another incurable cumulative neurodegenerative disorder characterized by both motor and nonmotor symptoms like Alzheimer's disease [12, 13]. Like AD the etiology of PD is also unknown, and it is believed that age, genetic and environmental factors are the reasons underlying the disease. The motor features include loss of striatal dopaminergic neurons and the nonmotor symptoms are responsible for the neuronal loss in nondopaminergic areas [12, 14]. Inflammation, oxidative stress, excitotoxicity, and reduced protein degradation, with mitochondrial dysfunction at the core, are the underlying mechanism of neurodegeneration [15]. As inflammation and oxidative stress add to the pathogenesis of PD, NSAIDs can beat against the root cause of disease as the currently available treatments only provide symptomatic relief [12].

Amyotrophic lateral sclerosis (ALS)

ALS is also another progressive disorder marked by the degeneration of upper and lower motor neurons in the brain and spinal cord that supply voluntary neurons. The medulla and anterior horn of the spinal cord were affected in the case of lower motor neurons while in the case of the upper motor neuron, the cerebral cortex. Patients suffering from ALS undergo progressive muscle weakness and finally end up with death, usually due to respiratory failure [16]. The word 'Amyotrophy' indicates the atrophy of muscle fibers as the anterior horn cells degenerate the muscle fibers that then get denervated, which finally leads to weakness of affected muscles and visible fasciculations, while 'Lateral sclerosis' is the hardening of anterior and lateral corticospinal tracts as motor neurons degenerate and are replaced by gliosis [17].

Prion diseases

Prion disease can be defined as a set of neurodegenerative diseases caused by abnormally shaped proteins called prions, that occur in sporadic (Jakob-Creutzfeldt disease), Gerstmann-Sträussler-Scheinker syndrome, genetic (genetic Jakob-Creutzfeldt disease, and fatal familial insomnia), and acquired (kuru, variant Jakob-Creutzfeldt disease, and iatrogenic Jakob-Creutzfeldt disease) forms, and the most common form that affects humans is Creutzfeldt-Jakob disease (CJD)[18].

Huntington disease

Huntington illness is a rare, incurable neurodegenerative disorder that affects the CNS. The symptoms include unwanted choreatic movements, dementia, behavioral and psychiatric disturbances. It is an autosomal dominant inherited disorder with continuous brain degeneration causing fast deterioration and eventually death. The most common cause of death is pneumonia, followed by suicide. The major population that is affected by the disease is the age group of 30-50 y [19].

Mechanism of neurological diseases

In all cases of neurodegenerative disorders, neuroinflammation is the underlying reason [20]. Some cerebral MR anomalies can be seen in patients suffering from neurodegenerative disorders. As a result of neuroinflammation, the immune cells in the circulatory system take up the central nervous system (CNS) and may constitute evidence for neural parenchymal damage. Also, the accumulated microglia surrounding the plaques, a local cytokine-mediated acute-phase reaction, and initiation of the complement cascade are contributed to neuropathological characteristics. These pathological hallmarks may harm the neurons and the inflammatory responses can be inhibited by NSAIDs, which can regulate the levels of COX-1 and COX-2 by triggering Peroxisome proliferator-activated receptor gamma (PPARγ) [21]. As this inevitable relationship between neuroinflammation and neurodegenerative disorder is well-established, [22] NSAIDs can be recommended for NDs [20]. The level of cyclooxygenase enzymes like COX-1 and COX-2 will be high in conditions like neurodegenerative diseases, traumatic brain injury, and ischemic diseases [23]. The inflammatory cytokines get elevated and thereby, the PGE level also increased along with the induction of COX-2 [20]. Moreover, in astrocytes, the pro-inflammatory cytokines can induce the expression of nitric oxide synthase and the activity of COX-2 [24]. Along with neuroinflammation, oxidative stress also prompts neurodegeneration. Free oxygen radicals, and consequently oxidative stress, trigger an increase in neurodegeneration [25, 26].

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that produces their activity by inhibiting prostanoids through inhibition of cyclo-oxygenase enzymes. For many years, it has been popularly used for the treatment of disease conditions such as fever, arthritis, to reduce pain, inflammation, and to prevent the formation of blood clots [27]. Since 1990, researches have been actively going on to establish the relationship between NSAIDs and neurological disorders [28]. The first hint that NSAIDs can reduce the chance of AD was made from the observation of patients who under the treatment of NSAIDs for rheumatoid arthritis had a serendipitous low incidence of dementia [29].

NSAIDs in the prevention and treatment of Alzheimer's disease

Indomethacin, a well-established NSAID with the ability to cross the blood-brain barrier, reported an acceptable result on 6 mo, double-blind, placebo-controlled study. About 44 patients with probable AD and a Mini-Mental State Examination (MMSE) score of 16 or more were included in this study. Efficiency was measured by considering the changes in the cognitive status score during the 6 mo of treatment and it is mentioned that the major dropout is due to gastrointestinal irritability. This study concluded with the 100-150 mg/d dose of Indomethacin exhibited neuroprotective activity in mild to moderate AD patients in comparison with placebo patients [8]. A double-blind, randomized placebo-controlled trial of indomethacin suggested that NSAIDs were not effective for the treatment of AD. 51 patients with mild to moderate AD were selected for this study in which 26 patients were administered with 50 mg twice-daily dose of the drug [30].

Even though it is unclear whether COX-1, COX-2, or both produced the neuroprotective activity, but Nimesulide a preferential COX-2 inhibitor, showed satisfactory results in a randomized pilot study. Studies were designed to measure both the effectiveness as well as the adverse events associated with the NSAID, Nimesulide, in AD patients. About 40 volunteers were subjected to a randomized pilot study by dividing them into two equal groups. The results were quite impressive on long term therapy and the adverse symptoms were found to be mild [31].

About 20 usually practicing NSAIDs were tested for the effects onamyloid beta-peptide 42(Aβ42) in cell culture, and some of them showed better activity by lowering the Aβ42. These categories of NSAIDs were tested on transgenic mice, and in the final results, Indomethacin, Diclofenac, Diflunisal, Flurbiprofen, Ibuprofen, Fenoprofen, Meclofenamic acid, and Sulindac which, reduces Aβ42 levels in the brains of mice, while Nabumetone, Ketoprofen, Aspirin, and Naproxen, didn't regulate Aβ42 levels. This study suggests that recommended doses of some NSAIDs can lower the level of Aβ42. A mismatch was also found between the results obtained from cell culture study and animal study. This study also discussed the activity of R and S enantiomers of Flurbiprofen-they acted similarly against Aβ42, could target γ-secretase complex, and the nuclear factor kappa B (NF-κB) [32].

Mefenamic acid, an anthranilic acid derivative and a frequently prescribed NSAID, was found that it could diminish neuronal cell death prompt by $A\beta_{1-42}$ treatment. And also, Mefenamic acid was found to exhibits the ability to trim down reactive oxygen species (ROS) and nitric oxide accumulation. The therapeutic potential as well as the neuroprotective mechanism of Mefenamic acid, were established by conducting *in vitro* and *in vivo* studies. The *in vitro* study suggested that as a result of the inhibitory activity on ROS (reactive oxygen species) and nitric oxide accumulation, the Mefenamic acid can act against $A\beta_{1-42}$treatment or Swedish double

mutation of amyloid precursor protein (Swe-APP) orthe C-terminal fragments of APP (APP-CTs) expression by obstructing the cytochrome c release from mitochondria and also the caspase-3 stimulation. Adding up to this, cell survival is accelerated by the up regulation of the anti-apoptotic protein Bel-XL expression. Through the *in vivo* study on $A\beta_{1-42}$ pervaded Alzheimer's disease rat model, it is revealed that Mefenamic acid can improve cognitive function [33].

A 52 w, multicentre, randomized, double-blind, placebo-controlled, parallel-group study of a selective COX-2 inhibitor, Celecoxib, were carried out on patients with mild to moderate AD to determine whether the drug possesses any neuroprotective activity. This study is concluded that a 200 mg bid celecoxib could not contribute to any improvement in patients and it was also observed that adverse events like death happened during this study, as the selected population was elderly with other comorbidities that affected the result [34]. Even so, Celecoxib also showed some successful outcomes inan18-month randomized, double-blind, placebo-controlled, parallel-group trial. A daily dose of either 200 or 400 mg was given to a population of 40-80 y age group with mild self-reported memory complaints. During the study, the participants experienced adverse events like gastrointestinal side effects. Despite these adverse effects the daily use of Celecoxib ameliorates cognitive functioning [35] and improves the prefrontal regional glucose metabolism. The study concluded that NSAIDs may have the ability to improve the cognitive functions in people with somewhat mild age-related cognitive complaints possibly before the neurological changes arise [36].

Ibuprofen, a propionic acid derivative, was analyzed for determination of the exact mechanism of action by usingisobaric tags for relative and absolute quantification (iTRAQ) coupled2-DLC-MS/M Sanalysis and is the fundamental investigation of neuroblastoma cells where the S, as well as the R enantiomer of Ibuprofen, were tested in which the S enantiomer is come up with neuroprotective activity by regulating oxidative stress and by down regulating the Cyclophilin A (CYP-A) expression. On that account, the study suggests that via several cellular pathways, Ibuprofen can lessen the risk of AD [37]. Based on the epidemiological evidence, a 12-month multicentre, randomized, double-blind, placebo-controlled, parallel-group trial was carried out on 132 patients who were diagnosed with mild to moderate AD in the age group of 65 and above. About 400 mg Ibuprofen bds or placebo along with 20 mg od of Esomeprazole or placebo was administered in randomly distributed groups. Among this, 70% of both groups completed the study with identical Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-cog) score worsening, indicating that either Ibuprofen is not effective in the tertiary precaution of mild to moderate AD or the 12-month study is not enough to prove the assumption [38]. A prophylactic treatment study of Ibuprofen on young triple transgenic (3XTg)-AD mice demonstrated a significant reduction of intraneuronal Aβ accumulation, improved cognitive performance, and also arrest the hyperphosphorylated tau immunoreactivity. Ibuprofen is administered as Ibuprofen supplemented chow to the 3XTg-AD mice, and the treated group has shown improved learning activity similar to the age-matched wild type. Simultaneously the untreated group came out with a remarkable disability to learn theMorris water maze (MWM) task. MWM is extremely reliant on hippocampal integrity and which is also considered as an estimate for the deficit in spatial reference and memory [39].

As per the previous reports, studies recommend that NSAIDs exert their neuroprotective activity by activated microglia and impaired Aβ accumulation especially the $A\beta_{42}$ species in the brain. The Cardiovascular health cognition study was conducted on 3229, 65, and above aged community free of dementia at baseline using NSAIDs, Aspirin, and Acetaminophen. In which NSAID users exhibited a lowered probability of every kind of dementia especially associated with AD in individuals with one or moreapolipoprotein E(APOE ε4) alleles. At the same time NSAIDs who reported with $A\beta_{42}$ reduction, activity doesn't show any superiority, while the Acetaminophen, as well as Aspirin, were not connected with any promising activity in this case [40].

Tarenflurbil, the R enantiomer of Flurbiprofen was previously reported as a selective $A\beta_{42}$ reducing agent (SALA) that also regulates the γ-secretase activity. A phase Ⅱ, a multicentre, randomized, double-blind, placebo-controlled, parallel-group study carried out in a population of 210 patients with a mini-mental state examination score of 15-26. The 800 mg dose of Tarenflurbil twice daily for 24 mo was reported with fewer functional ability in comparison with placebo [41].

The protective effect of NSAIDs was investigated by examining several case studies obtained from the US Veteran Affairs Health Care System. The community aged 55 y and above with reported AD were considered in this study. The population who received NSAIDs for a long period was at a lower risk of AD. The protective effects of different NSAIDs seem to be different, in which Ibuprofen has shown promising results through $A\beta_{42}$ regulation [42].

A recent study based on the hypothesis that NSAIDs can protect from AD incidence was manifested about a 71% reduction in the risk of death associated with AD in the aged population especially in Aspirin users [28].

A retrospective cohort study suggested that the frequency of incidence of AD is lowered in the case of Diclofenac when comparing to Naproxen and Etodolac. Diclofenac can actively transport across the blood-brain barrier (BBB) and activity is expected to be produced by lowering the level of amyloid-beta and interleukin 1 beta [43].

CONCLUSION

NSAIDs, the widely used Over the Counter medication, have been known for their neuroprotective activity for almost 30 y. From 1990-2020 there were several types of research were happened via epidemiological study, clinical trials, experiments on transgenic mice as well as *in vitro* studies. The results were so confusing because several contradictions were observed even for the same drug on the final reports. The majority of researches are concluded with a hopeful result in the area of neuroprotective activity of NSAIDs by *in vitro* as well as *in vivo* studies. Simultaneously some mismatches were also reported with the *in vitro* and *in vivo* study of the same drug. NSAIDs produce its neuroprotective activity by a wide range of mechanisms such as reducing neuroinflammation by regulating various inflammatory pathways, regulating the level of Aβ and tau proteins, preventing the accumulation of reactive oxygen species, and nitric oxide. During the period of several studies, some of the volunteers were withdrawn from the clinical trials and some are died due to the adverse events associated with NSAIDs.

In summary, the long-term treatment of NSAIDs only exhibited beneficiary activity against Alzheimer's disease. The impaired activity is due to the limited brain accessibility because of low lipophilicity. Hence, we recommend, drug modification methods such as the pro-drug approach thereby we can improve the lipophilicity of the drug as well as balance the adverse events like gastrointestinal irritability.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declared no conflict of interest.

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