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APPLICATIONS OF NASAL NSAIDS IN ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative diseases with age as the greatest risk factor. Epidemiological observation indicates that long-term oral administration of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen to patients having rheumatoid arthritis results in reduced risk and delayed onset of Alzheimer's disease. Alzheimer's disease starts in the entorhinal cortex, which is closely connected to the olfactory nerves, and spreads anatomically in a defined pattern. Therefore, a nasal NSAID would readily reach the region of the brain where it is most likely to be therapeutic. This study provides a general overview on the role of neuroinflammation in these neurodegenerative diseases and an update on NSAID treatment in recent experimental animal models, epidemiological analyses and clinical trials.

KEYWORDS: Non-steroidal anti-inflammatory drugs, Alzheimer's disease, Parkinson's disease, cyclooxygenase, neuroinflammation, Prostaglandins etc.

1. INTRODUCTION

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and the most common cause of dementia. An estimated 5.2 million Americans from different age-groups have AD in 2013. The total number of patients with AD dementia in 2050 is projected to be 13.8 million, with 7.0 million aged 85 years or older. Only symptomatic relief is being offered by the current therapeutic interventions and none being able to halt disease progression or reverse its symptoms. Cholinesterase inhibitors have consistently shown symptomatic benefits and arenow recognized as the standard treatment in patients with mild to moderate AD.[1]

The role of inflammation in AD has been extensively studied over the last 2 decades pointing toward a central role of inflammation in AD pathogenesis. Microglia, the primary immune cells of the brain, is activated in AD and is predictive of symptom severity. The role of inflammatory mediators in AD-associated dysfunction of neuro supportive cells like astrocytes and oligodendrocytes has been established by the several studies. Also, results from preclinical studies indicated the effect of immune proteins like cytokine and chemokine on amyloidosis, neurodegeneration, and cognition. These studies provide evidence that inflammation plays a significant role in pathophysiology of AD.

Among the anti-inflammatory compounds, non-steroidalanti-inflammatory drugs (NSAIDs) were considered the mostpromising by these studies. Although several distinct actionshave been described for the mechanism of action of NSAIDs, the classical NSAIDs primarily inhibit cyclooxygenase (COX)activity. Although both COX-1 and COX-2 are expressed in the brain under normal conditions, the localization of COX-1 in microglia and the regulation of COX-2 by inflammatory mediators suggest that these enzymes could be involved in the neuroinflammatory response in AD.

According to the United States Centers for Disease Control and Prevention, the average American lifespan has increased from 73.7 years (1980) to 77.9 years (2007). Aging is associated with increased risk of neurological disease or disorder, including Alzheimer's disease (AD) and Parkinson's disease (PD). Collectively, these neurodegenerative diseases are estimated to impact over 10% of the US population >60 years of age, at an annual cost beyond $30 billion USD related to medical care, lost.[2]

2. ALZHEIMER'S DISEASE

These are a heterogenous group of drugs developed for use in dementia and other cerebral disorders. They do elicit pharmacological effects, but widely different mechanisms of action are claimed and therapeutic benefits are uncertain.

Dementia:-Refers to acquired global impairment of intellect, memory and personality (cognitive functions) in the absence of gross clouding of consciousness or motor involvement. Memory, capacity to solve problems of day to day living, performance of learned motor skills, social skills and control of emotions are primarily affected.

Alzheimer's Disease (AD):-A progressive neurodegenerative disorder which affects older individuals and is the most common cause of dementia. It may progress to a totally vegetative state. Atrophy of cortical and subcortical areas is associated with deposition of β-amyloid protein in the form of senile plaques, and formation of neurofibrillary tangles. There is marked cholinergic deficiency in the brain, though other neurotransmitter systems are also affected.

The indications of cognition enhancers include.

1. Senile dementia of Alzheimer type (DAT) andmulti infarct dementia (MID).
2. Common symptoms of the elderly dizzinessand memory disturbances.
3. Mental retardation in children, learningdefects, attention deficit disorder.

Alzheimer's disease, named after the doctor who first described it (Alois Alzheimer), is a physical disease that affects the brain. There are more than 520,000 people in the UK with Alzheimer's disease. During the course of the disease, proteins build up in the brain to form structures called 'plaques' and 'tangle'. This leads to the loss of connections between nerve cells, and eventually to the death of nerve cells and loss of brain tissue. People with Alzheimer's also have a shortage of some important chemicals in their brain. These chemical messengers help to transmit signals around the brain. When there is a shortage of them, the signals are not transmitted as effectively. As discussed below, current treatments for Alzheimer's disease can help boost the levels of chemical messengers in the brain, which can help with some of the symptoms. Alzheimer's is a progressive disease. This means that gradually, over time, more parts of the brain are damaged. As this happens, more symptoms develop. They also become more severe.[3]

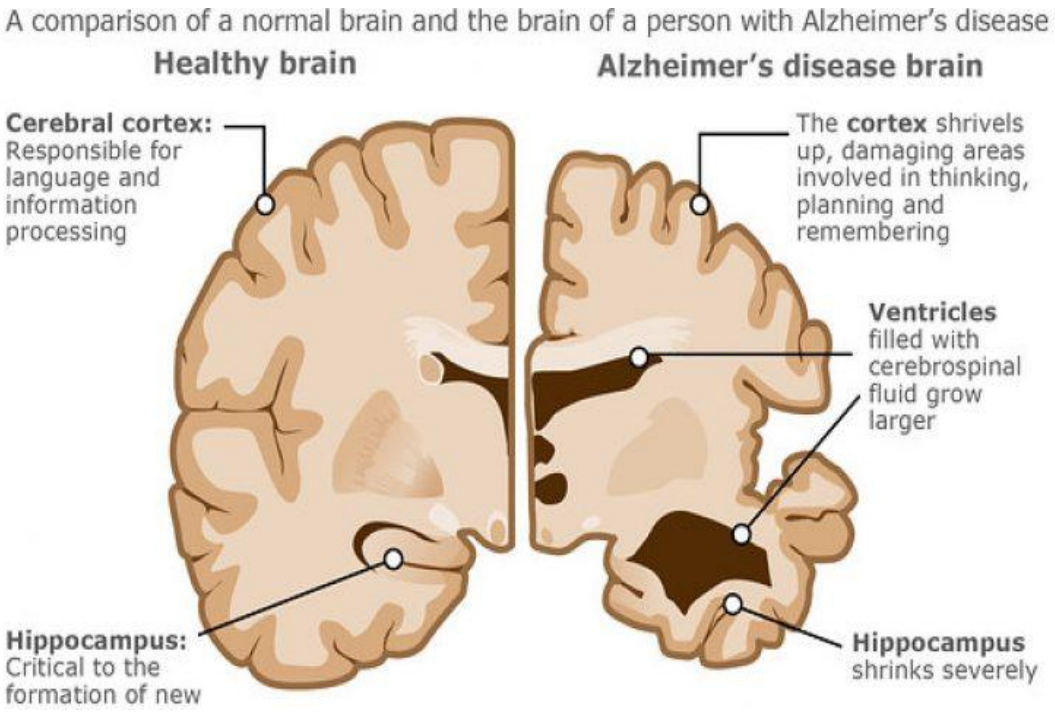

Figure 1: Comparison between Brain of normal person & brain of person with Alzheimer's disease.

3. SIGN & SYMPTOMS

The symptoms of Alzheimer's disease are generally mild to start with, but they get worse over time and start to interfere with daily life.

There are some common symptoms of Alzheimer's disease, but it is important to remember that everyone is unique. Two people with Alzheimer's are unlikely to experience the condition in exactly the same way.

For most people with Alzheimer's, the earliest symptoms are memory lapses. In particular, they may have difficulty recalling recent events and learning new information. These symptoms occur because the early damage in Alzheimer's is usually to a part of the brain called the hippocampus, which has a central role in day-to-day memory. Memory for life events that happened a long time ago is often unaffected in the early stages of the disease.

Although memory difficulties are usually the earliest symptoms of Alzheimer's, someone with the disease will also haveor go on to develop problems with other aspects of thinking, reasoning, perception or communication.

They might have difficulties with

- Language – struggling to follow a conversation or repeating themselves.
- Visuospatial skills – problems judging distance or seeing objects in three dimensionsnavigating stairs or parking the car become much harder.
- Concentrating, planning or organizing – difficulties making decisions, solving problems or carrying out a sequence of task (such as cooking ameal).
- Orientation – becoming confused or losing track of the day or date.

A person in the earlier stages of Alzheimer's will often have changes in their mood. They may become anxious, irritable or depressed. Many people become withdrawn and lose interest in activities and hobbies.

3.1 LATER STAGE

As Alzheimer's progresses, problems with memory loss communication, reasoning 5and orientation become more severe. The person will need more day-to-day support from those who care for them. Some people start to believe things that are untrue (delusions) or less often see or hear things which are not really there (hallucinations). Many people with Alzheimer's also develop behaviours that seem unusual or out of character. These include agitation (for example, restlessness or pacing), calling out, repeating the same question, disturbed sleep patterns or reacting aggressively. Such behaviours can be distressing or challenging for the person and theircareer.

They may require separate treatment and management to memory problems. In the later stages of Alzheimer's disease someone may become much less aware of what is happening around them. They may have difficulties eating or walking without help, and becomeincreasingly frail. Eventually, the person will need help with all their daily activities. How quickly Alzheimer's disease progresses, and the life expectancy of someone with it, vary greatly. On average, people with Alzheimer's disease live for eight to ten years after the first symptoms. However, this varies a lot, depending particularly on how old the person was when they first developed Alzheimer's.

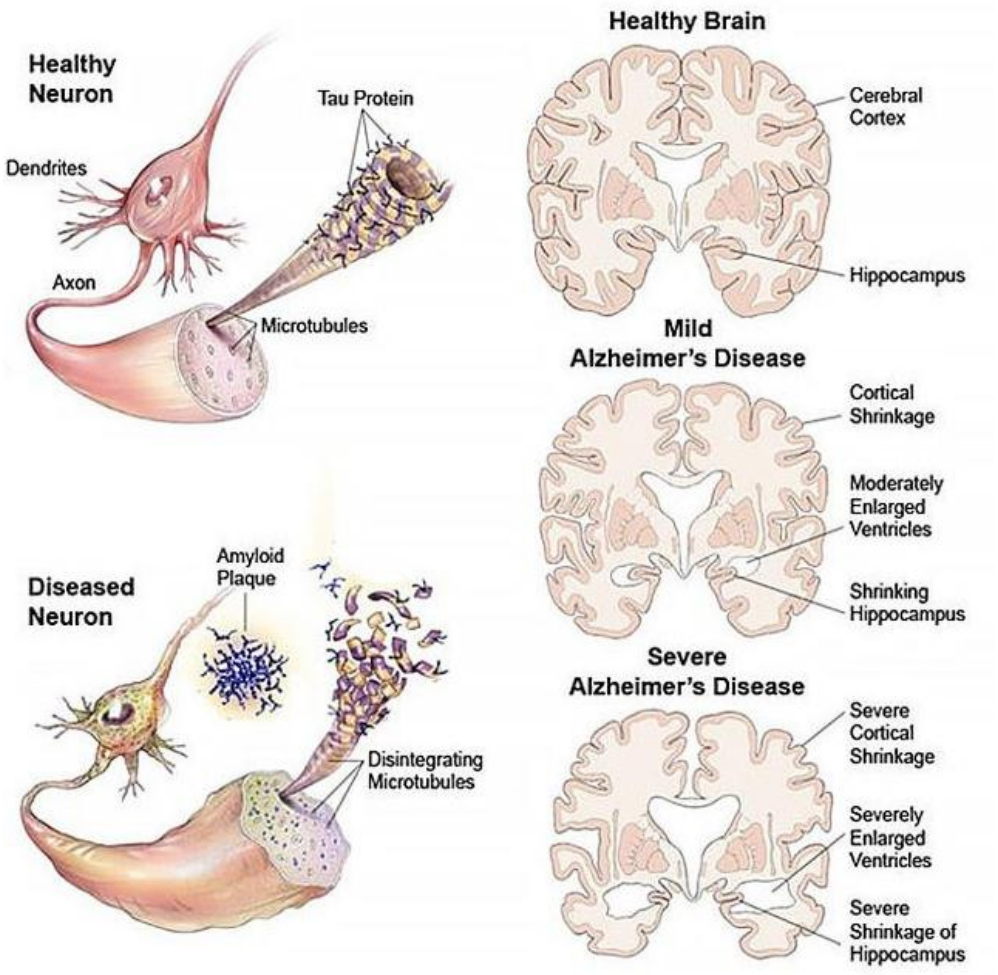

Figure 2: AD-Sign and Sypmtoms.

3.2 The progression of Alzheimer's disease and other dementias.

Mixed dementia

An estimated 10 per cent of people with dementia have more than one type at the same time. This is called mixed dementia. The most common combination is Alzheimer's disease with vascular dementia (caused by problems with the blood supply to the brain). The symptoms of this kind of mixed dementia are a mixture of the symptoms of Alzheimer's disease and vascular dementia.

Atypical Alzheimer's disease

In some people with Alzheimer's disease the earliest symptoms are not memory loss. This is called atypical Alzheimer's disease. The underlying damage (plaques and tangles) is the same, but the first part of the brain to be affected is not the hippocampus.

Atypical Alzheimer's disease is uncommon in those diagnosed when they are over 65. It accounts for around five per cent of all Alzheimer's in this age group. It is, however, more common in people diagnosed when they are under 65 (early-onset Alzheimer's disease). In this age group it represents up to one-third of cases.

The atypical forms of Alzheimer's disease are as follows.

- Posterior cortical atrophy (PCA) occurs when there is damage to areas at the back and upper-rear of the brain. These are areas that process visual information and deal with spatial awareness. This means the early symptoms of PCA are often problems identifying objects or reading, even if the eyes are healthy. Someone may also struggle to judge distances when going down stairs, or seem uncoordinated (for example when dressing).
- Logopenic aphasia involves damage to the areas in the left side of the brain that produce language. The person's speech becomes laboured with long pauses.
- Frontal variant Alzheimer's disease involves damage to the lobes at the front of the brain. The symptoms are problems with planning and decision-making. The person may also behave in socially inappropriate ways or seem not to care about the feelings of others.

4. Who gets Alzheimer's disease?

Most people who develop Alzheimer's disease do so after the age of 65, but people under this age can also develop it. This is called early-onset Alzheimer's disease, a type of young-onset dementia. In the UK there are over 40,000 people under the age of 65 with dementia. Developing Alzheimer's disease is linked to a combination of factors, explained in more detail below. Some of these risk factors (such as lifestyle) can be controlled, but others (such as age and genes) cannot. The major factor considered for AD is age above 65, hence it is was a risk factor for AD.

5. Risk factors for dementia

Age

Age is the greatest risk factor for Alzheimer's. The disease mainly affects people over 65. Above this age, a person's risk of developing Alzheimer's disease doubles approximately every five years. One in six people over 80 have dementia.

Gender

For reasons that are not clear, there are about twice as many women as men over 65 with Alzheimer's disease. This difference is not fully explained by the fact that women on average

live longer than men. It may be that Alzheimer's in women is linked to a lack of the hormone oestrogen after the menopause.

Genetic inheritance

Many people fear that the disease may be passed down to them from a parent or grandparent. Scientists are investigating the genetic background to Alzheimer's. There are a few families with a very clear inheritance of Alzheimer's from one generation to the next. In such families the dementia tends to develop well before age 65. However, Alzheimer's disease that is so strongly inherited is extremely rare.

In the vast majority of people, the influence of genetics on risk of Alzheimer's disease is much more subtle. A number of genes are known to increase or reduce a person's chances of developing Alzheimer's. For someone with a close relative (parent or sibling) who was diagnosed with Alzheimer's when over 65, their own risk of developing the disease is increased. However, this does not mean that Alzheimer's is inevitable, and everyone can reduce their risk by living a healthy lifestyle. People with Down's syndrome are at particular risk of developing Alzheimer's disease, because of a difference in their genetic makeup.

Health and lifestyle

Medical conditions such as diabetes, stroke and heart problems, as well as high blood pressure, high cholesterol and obesity in mid-life, are all known to increase the risk of both Alzheimer's disease and vascular dementia. Anyone can reduce their risk by keeping these under control. Depression is a probable risk factor for dementia; getting it treated early is important. People who adopt a healthy lifestyle, especially from mid-life onwards, are less likely to develop Alzheimer's disease. This means taking regular physical exercise and keeping to a healthy weight, not smoking, eating a healthy balanced diet and drinking only in moderation. Leading an active lifestyle that combines regular physical, social and mental activity will help to lower risk.

Table 1: Clinical criteria for dementia.[4]

1.	Progressive impairment in two or more areas of cognition:
A)	Memory (ability to learn and remember new information)
B)	Language (speaking, reading, writing)
C)	Executive function (reasoning, decision making,planning)
D)	Visuospatial function (ability to recognize faces and objects)
E)	Praxis (ability to perform purposeful movements)
F)	Praxis (ability to perform purposeful movements)

2)	Cognitive deficits:
A)	Interfere with functioning (ability to perform activities ofdaily living)
B)	Represent a decline from previous levels of functioning
C)	Are not due to delirium or psychiatric disorder (e.g.,depression)
D)	Are established using history from patient, corroboratedby informant (e.g., familymember), and objective cognitiveassessment.

6. Diagnosis

Anyone who is concerned that they may have Alzheimer's disease (or any other form of dementia) should seek help from their GP. If someone does have dementia, an early diagnosis has many benefits: it provides an explanation for the person's symptoms; it gives access to treatment, advice and support; and it allows them to prepare for the future and plan ahead. There is no single test for Alzheimer's disease. The GP will first need to rule out conditions that can have similar symptoms, such as infections, vitamin and thyroid deficiencies (from a blood test), depression and side effects of medication. The doctor will also talk to the person, and where possible someone who knows them well, about their medical history and how their symptoms are affecting their life. The GP or a practice nurse may ask the person to do some tests of mental abilities.

The GP may feel able to make a diagnosis of Alzheimer's at this stage. If not, they will generally refer the person to a specialist. This could be an old-age psychiatrist (who specialized in the mental health of older people) often based in a memory service. Or it might be a geriatrician (who specialized in the physical health of older people), a neurologist (who specialized in conditions of the brain and nervous system) or a general adult psychiatrist (who specialized in mental health in adults) in a hospital. The specialist will assess the person's symptoms, and how they developed, in more detail. In Alzheimer's disease there will usually have been a gradual worsening of memory over several months. A family member may be more aware of these changes than the person with suspected Alzheimer's is themselves.

The person's memory, thinking and other mental abilities will also be assessed further with a pen-and-paper test. When someone with Alzheimer's is tested, they will often forget things quite quickly. They will often not be able to recall them a few minutes later even when prompted.

The person may undergo a brain scan, which can show whether certain changes have taken place in the brain. There are a number of different types of brain scan. The most widely used are CT (computerized tomography) and MRI (magnetic resonance imaging). A brain scan

may rule out certain conditions such as stroke, tumor or a build-up of fluid inside the brain. These can have symptoms similar to those of Alzheimer's. It may also clarify the type of dementia. In a person with early Alzheimer's disease a brain scan may show that the hippocampus and surrounding brain tissue have shrunk. The diagnosis should be communicated clearly to the person and usually also to those closest to them, along with a discussion about the next steps.[4]

7. Neuropathology of AD

At the cellular level, AD is characterizedby a progressive loss of cortical neurons, especially pyramidal cells, that mediate higher cognitivefunctions. Substantial evidence also suggests that AD causes synaptic dysfunction early in the disease process, disrupting communication within neural circuitsimportant for memory and other cognitive functions.AD-related degeneration begins in the medial temporallobe, specifically in the entorhinal cortex and hippocampus Damage to these brain structures results in memory and learning deficits that are classically observed with early clinical manifestations of AD. The degeneration then spreads throughout the temporalassociation cortex and to parietal areas. As the disease progresses, degeneration can be seen in the frontalcortex and eventually throughout most of the remainingneo-cortex. Of note is the fact that AD causes pronounced.

In addition to cognitive impairment across multiple domains (memory, language, reasoning, executive, and visuospatial function), patients with AD show an impaired ability to perform activities of daily living and often experience psychiatric, emotional, and personality disturbances. It has been theorized that the neuronal damage seen in AD is related to the deposition of abnormal proteins both within and outside of neurons. These are the hallmark pathological lesions of AD known as 'plaquesand tangles.' The abnormal proteins are deposited in the cerebral cortex following a stereotypical pattern of spread along neural pathways that mediate memory and other cognitive functions. 'Senile plaques' are extracellular accumulations of amyloid protein and consist of insoluble amyloid-beta protein (Ab). Normally, cells throughout life release soluble Ab after cleavage of the APP- a cell surface receptor. AD involves abnormal cleavage of APP that results in the precipitation of Ab into dense beta sheets and formation of senile plaques. It is believed that microglia and astrocytes then mount an inflammatory response to clear the amyloid aggregatesand this inflammation likely causes destruction of adjacent neurons and their neurites (axons and dendrites).'Neurofibrillary tangles' (NFT) are intracellular aggregates of abnormally hyper-

phosphorylated protein tau, which in normal form serves as a microtubule stabilizing protein and plays a role in intracellular (axonaland vesicular) transport. It is possible that NFT interfere with normal axonal transport of components necessary for proper neuronal function and survival (e.g., synaptic vesicles with neurotransmitters, neurotrophic factors, and mitochondria), eventually causing neurons to die. Substantial evidence supports the idea that amyloid formation and deposition in the cerebral cortex is one of the earliest pathological processes in AD, preceding the clinical onset of the disease by 10-20 years. Despite this, the temporal sequence of events in the deposition of amyloid plaques and formation of NFT during development of AD remains open to debate. In fact, a recent study suggests that the initial formation of NFT may occur in the brainstem rather than the medialtemporal lobe and may precede the appearance of the first amyloid plaques in the neo-cortexand this inflammation likely causes destruction ofadjacent neurons and their neurites (axons and dendrites). 'Neurofibrillary tangles' (NFT) are intracellular aggregates of abnormally hyper-phosphorylated protein-tau, which in normal form serves as a microtubule estabilizing protein and plays a role in intracellular (axonaland vesicular) transport Substantial evidence supports the idea thatamyloid formation and deposition in the cerebral cortexis one of the earliest pathological processes in AD, preceding the clinical onset of the disease by 10-20years. Despite this, the temporal sequence of events inthe deposition of amyloid plaques and formation of NFTduring development of AD remains open to debate. Infact, a recent study suggests that the initial formation of NFT may occur in the brainstem rather than the medialtemporal lobe and may precede the appearance of thefirst amyloid plaques in the neocortex. The table N0. 2 shows various type of dementia according to their vascular system, lewy body and frontotemporal dementia.[5]

Table 2: Clinical features that distinguish AD from other dementias.

Clinical feature	Alzheimer's dementia	Vascular dementia	Parkinson's dementia	Dementia with Lewy bodies	Fronto-temporal dementia
Patient profile	65 years old	40 years old Vascular risk	65 years old	75 years old (mean)	50-70 years old
History	Gradual onset and deterioration	Acute onset, stepwise deterioration	Gradual onset and deterioration	Gradual onset and deterioration	Gradual onset And deteriorate-on
Initial symptoms	Memory loss	Executive dysfunction	Visual hallucinations	Visual hallucinations, fluctuating attention	Memory intact Disinhibition, apathy or aphasia
Physical findings	No motor impairment (untillate stage)	Pyramidal (uppermotor neuron)signs	Parkinsonism (precedes dementia by -1 year)	Parkinsonism (presents within 1 year of dementia)	Usually none.

8. DRUG USED IN AD

The cerebro-active drugs may be grouped into:

a. Cholinergic activators: Tacrine, Rivastigmine, Donepezil.
b. Glutamate (NMDA) antagonist: Memantine
c. Miscellaneous cerebro-active drugs: Piracetam, Pyritinol (Pyrithioxine), Dihydro-ergotoxine (Codergocrine).

Cholinergic activators: - Since brain Ach levels are markedly reduced and cholinergic neurotransmission is the major sufferer in AD, various approaches to augment brain ACh have been tried. Precursor loading with choline or lecithin have failed because there is no shortage of these substrates in the brain. Cholinergic agonists (arecoline, bethanechol, oxotremorine) and conventional anticholinesterases (anti-ChEs) like physostigmine produce symptom improvement, but at the cost of marked peripheral side effects. Over the past decade cerebroselectiveanti ChEs have been introduced for use in AD.

Tacrine: - It is the first centrally acting anti-ChE to be introduced for AD. In clinical trials tacrine produced significant improvement in memory, attention, praxis, reason and language. However, it does not alter course of the underlying disease process. Frequent side effects and hepatotoxicity have restricted its use.

Rivastigmine:- This carbamate derivative of physostigmine inhibits both AChE and BuChE, but is more selective for the G1 isoform of AChE that predominates in certain areas of the brain.

Rivastigmine is highly lipid-solubleenters brain easily. Greater augmentation of cholinergic transmission in brain is obtained with mild peripheral effect. The carbamoyl residue introduced by rivastigmine into AChE dissociates slowly resulting in inhibition of cerebral AChE for upto 10 hours despite the 2 hr plasma t½ of the drug.

In clinical trials an average of 3.8 point improvement in Alzheimer's disease Assessment Scale (ADAS-cog) has been obtained compared to placebo. Other symptoms like apathy, delusions, hallucinations and agitation also improve, though disease progression is not affected. Peripheral cholinergic side effects are mild. It has not produced liver damage Dose: Initially 1.5 mg BD, increase every 2 weeks by 1.5 mg/day upto 6 mg/BD. EXELON, RIVAMER 1.5, 3, 4.5, 6.0 mg caps.

Donepezil:- This cerebroselective and reversible anti-AChE produces measurable improvement in several cognitive as well as non-cognitive (activities of daily living) scores in AD, which is maintained at least upto 2 years. The benefit isascribed to elevation of ACh level in the cortex, especially in the surviving neurones that projectfrom basal forebrain to cerebral cortex and hippocampus. Therapeutic doses produce only weak peripheral AChE inhibition: cholinergic side effects are mild. Because of long t½ (~70 hr), donepezil is administered once daily at bed time; a distinct advantage over rivastigmine and galantamine which need twice daily dosing. It is generally well tolerated and is not hepatotoxic.

Memantine:- This new NMDA receptorantagonist, related to amantadine (alsoa NMDAantagonist), has been found to slow thefunctional decline inmoderate-to-severe AD, butbenefit in milder disease are unclear. It appearstoblock excitotoxicity of the transmitter glutamatein a noncompetitive and usedependentmanner. Beneficial effects have also been notedin parkinsonism. Memantine is better tolerated than anti-AchEs used in AD. Side effects areconstipation, tiredness, headache and drowsiness. It is indicated in moderate-to-severe AD.[5]

9. APPLICATION OF NSAIDs IN AD

Although the etiology and behavioral symptoms differ among neurodegenerative diseases, neuroinflammation is a feature of both AD and PD. Neuroinflammation, as characterized by activation of glia (gliosis) and elevated presence of inflammatory molecules, is a common component of the normal aging brain, yet is exacerbated in AD and PD. Analogous to stimulated macrophages in peripheral immune responses, reactive microglia mediate central nervous system (CNS) immune responses through the phagocytosis of necrotic material and the release of pro-inflammatory signals to initiate "wound healing". In this respect, it is not surprising to observe inflammatory markers in conjunction with disease pathology and microglia containing fragments of cellular debris in regions of neurodegeneration. Although assumed to be a local tissue response to combat the condition-specific pathology, neuroinflammation independently appears to actively contribute to CNS pathophysiology. Consideration of age-associated reactive gliosis in light of epidemiological studies reporting reduced risk of AD in patients with chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) has spurred intense research to investigate the implications of neuroinflammation. Furthermore, the development of specific NSAIDs and the recognition of NSAIDs targets in the diseased brain have fueled a wide range of animal and clinical studies. This overview will

provide an update on the understanding of neuroinflammation's role in selected neurodegenerative diseases by highlighting experimental and clinical results that illustrate the impact of NSAIDs administration on AD and PD progression.[6]

10. Mechanism of Action of NSAIDs

Rubor (redness), calor (heat), tumour (swelling), and dolor (pain) were the cardinal signs of inflammation described by the Romans (30–40 B.C.). The use of medicines to alleviate peripheral inflammation is one of the oldest therapies on record, with chewing of willow leaves and bark prescribed by Hippocrates to reduce pain, swelling, and fever. Although the active ingredient in willow bark extract, salicin, was isolated in the early 19th century and mass distributed as acetylsalicylic acid under the brand name Aspirin® (Bayer) by the end of the century, the mechanism by which this NSAIDs relieved inflammatory symptoms was unknown.

In 1991, molecular studies revealed that the COX enzyme exists in multiple isoforms, identified as COX-1 and COX-2 In addition, tissue-specific expression of COX-3, an additional isoform produced by a splice variant of COX-1, was described in 2002 however it is not believed to contribute to PG production and will not be considered further in this review. The amino acid sequences of COX-1 and COX-2 are more than 60% identical, governing similar overall structure. When considering genetic sequences, COX-2 has a unique promoter region that allows upregulation of expression by growth factors, tumor promoters, hormones, bacterial endotoxin, cytokines, anoxia, neurotoxins, electrical stimulation, and pro-inflammatory stimuli. Therefore, it has been accepted that COX-1 is constitutively expressed whereas COX-2 is expressed as part of the inflammatory response in most tissues. However, these traditional roles of COX isoform expression are not observed in the brain as COX-2 mRNA and protein are detectable in neurons in absence of inflammatory stimulus and COX-1 has been reported to contribute to elevations of PGE2 in experimental models of neuro-inflammation.

Although having effective anti-pyretic, anti-inflammatory, anti-thrombotic and analgesic properties, chronic aspirin use was associated with GI discomfort, ulcers, and bleeding due to reduction of prostaglandins required for normal physiology. Pharmacological analysis determined that the acetyl group of aspirin irreversibly inhibits COX from binding AA. The introduction of ibuprofen, a reversible non-specific COX inhibitor, provided an alternative NSAIDs with reduced side effects. However, the discovery of COX-2 as the inducible and

pro-inflammatory enzyme isoform fueled intense work to develop COX-2 selective inhibitors for maximum inflammation resolution with minimal gastric side effects. X-ray crystallography data has shown that the COX-2 isoform contains a small structural difference in the binding site of arachidonic acid; it contains an extended pocket in the binding site, which allows COX-2 selective inhibitors to be constructed with a pro-turbance that would fit into this pocket.

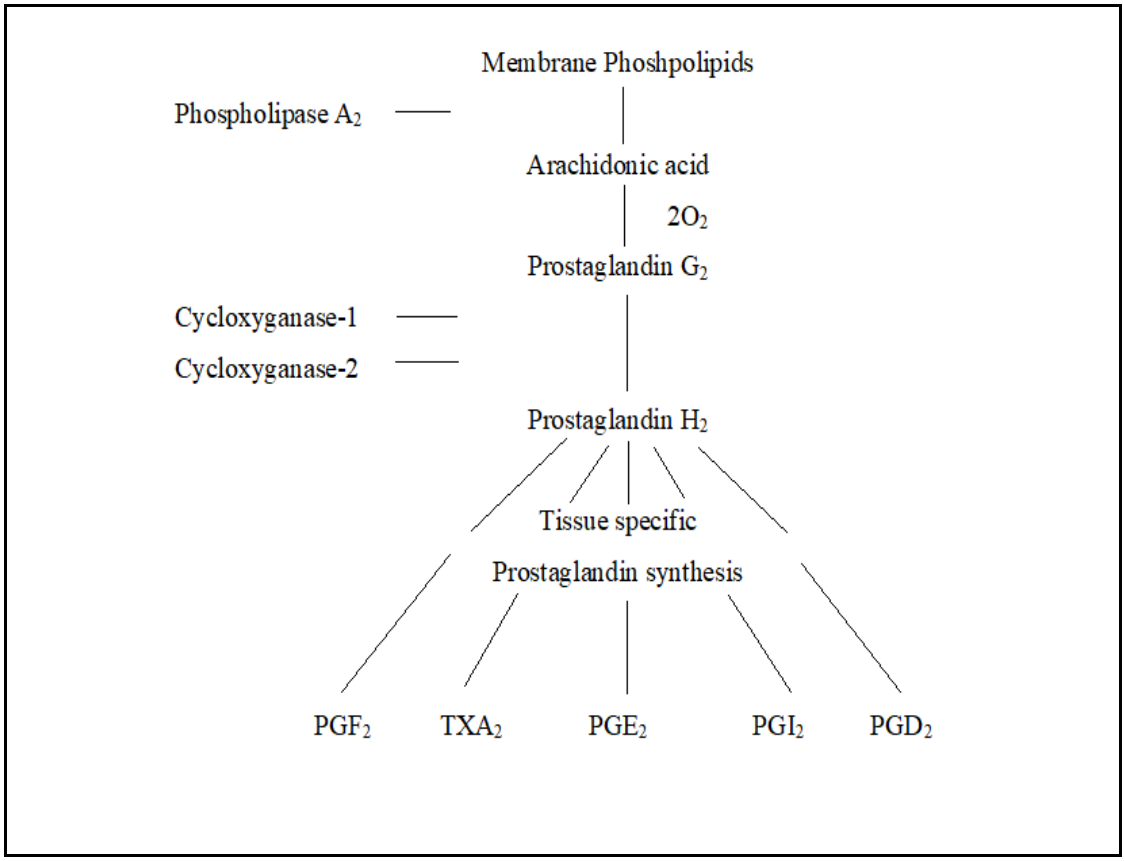

Figure 3: Prostaglandin synthesis with attention to COX expression in neural cells.

Many COX-2 selective inhibitors contain a 4-methylsulfonyl or sulfonamide substiuent on a cis-stilbene moiety that fits into this pocket. Examples of drugs in this class include NS398, DuP697, celecoxib, rofecoxib, and valdecoxib with varying selectivies for COX-2. The synthesis of prostanoids (prostaglandins and thromboxanes), a group of potent lipid mediators acting in diverse physiological processes, is dependent on the enzymatic activity of cyclooxygenase (COX).

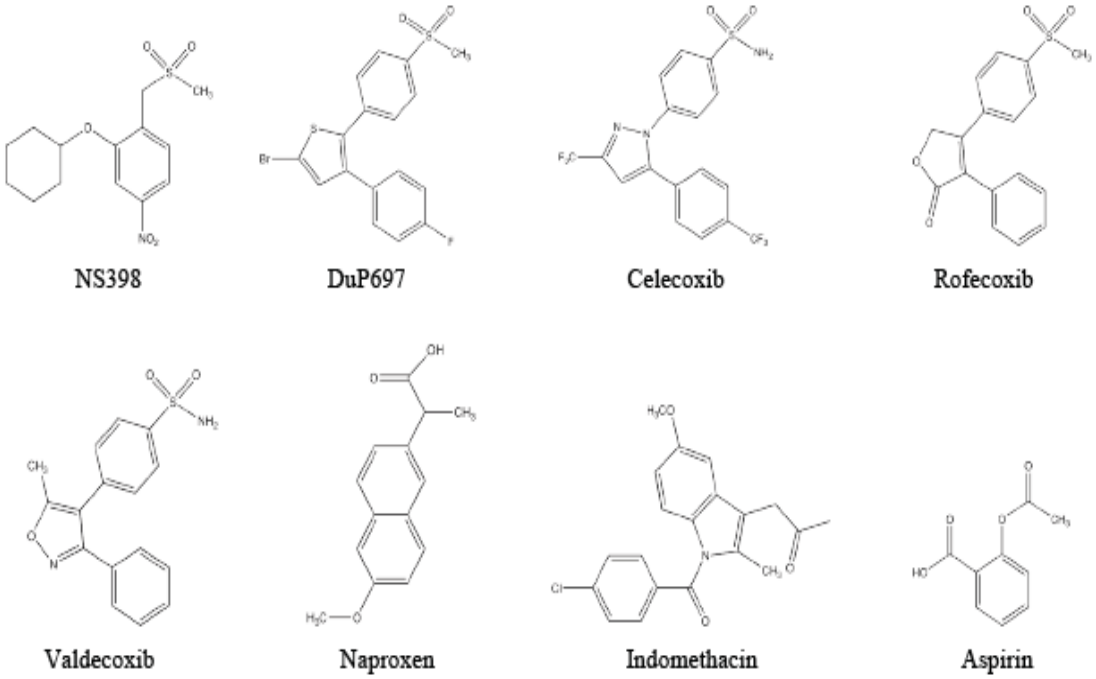

Figure 4: Chemical structures of common NSAIDs.[2]

11. Animal models investigating neuroinflammation in AD

When epidemiological studies reported that chronic NSAIDs use reduces risk for AD, increasing attention was focused on markers of neuroinflammation in the AD brain. Numerous rodent models have been utilized to better understand the relationship between inflammatory mediators and pathology observed in post-mortem brain from dementia and AD patients, including direct administration of Aβ, infusion of pro-inflammatory agents to brain, and genetically modified rodent strains that over- or under-express the pathological markers of AD and their precursors. The majority of these models shows reactive gliosis and altered brain expression of COX-2 that accompanies pathology and behavioral dysfunction. Considerable evidence suggests that the increase in COX-2 in such models is due to both direct and indirect activation of microglia by A. In addition to microgliosis, elevated COX-1 and COX-2 protein levels are observed in post-mortem AD brain compared to age-matched, non-demented controls. Specifically, neuronal COX-2 expression in the hippocampus directly correlates with the severity of the dementia and COX-2 immunoreactivity in the CA1 correlates strongly with AD plaque and neurofibrillary tangle density.

As age is a risk factor for AD and an increase in glial activation has been observed in aged brain, studies have attempted to ascertain the causal relationship between neuroinflammatory

markers and pathological markers for AD. Rodent models of chronic neuroinflammation have demonstrated induction of AD-like molecular and cellular changes and spatial memory deficits. Furthermore, glial activation can be observed prior to the detection of tau-related neurofibrillary tanglesand induction of neuroinflammation by both pro-inflammatory stimulus lipopolysaccharide (LPS) and IL-1 increase the rate of tau phosphorylation, an intermediary step in the development of tangles.

Considering that COX-2 expression increases following microglial activation, it is of interest that transgenic mice over-expressing COX-2 developed an age-dependent deficit in spatial memory at 12 months and 20 months of age that was associated with remarkable neuronal apoptosis and astrocyctic activationresults that suggest an independent contribution of COX-2 activity in neurodegeneration that may impact progression of AD pathology. Deletion or antagonists of the PGE2 receptors EP2 and EP4, both in cultured cells expressing mutant amyloid precursor protein (APP)and *in vivo*, resulted in a significant reduction of beta-amyloid plaques, further confirming that Aβ and PGE2 synthesis are part of a positive feedback loop contributing to AD pathology.

To test this hypothesis, studies using AD animal models have incorporated NSAIDs administration, hypothesizing that inhibition of COX activity will reduce disease-associated pathology. For example, experiments have demonstrated that oral administration of ibuprofen, a non-specific COX inhibitor, at onset of amyloid plaque formation decreased glial activation and plaque density in transgenic mice over-expressing APP, a crucial determinant of Aβ fibrils. Indomethacin treatment attenuated microglial activation, restored disturbance in hippocampal long-term potentiation, and prevented working memory deficits associated with Aβ injections into the dentate gyrus of rats. Demonstrating the synergistic effects of inflammation and plaques, intracerebroventricular administration of Aβ induced increases in COX-2 levels and memory impairment that were magnified upon coincident intraperitoneal administration of LPS. These compounded alterations were attenuated by pre-treatment with NS398, a COX-2-selective inhibitor indicating that elevated COX-2 levels may be an intermediate between the pathological markers of AD and the common cognitive and behavioral symptoms.[2]

12. Clinical trials of NSAIDs in AD treatment and prevention

Both epidemiological and animal model research demonstrating benefits of NSAIDs treatment in AD provided justification for clinical trials in assessing the efficacy of COX

inhibitors (specific and non-specific) in the treatment or prevention of AD. In particular, the development of COX-2 inhibitors (coxibs) and the presence of elevated COX-2 in both post-mortem brain and AD animal models positioned this class of NSAIDs as promising therapy with minimal GI side effects. Despite this initial evidence of indomethacin having beneficial effects in slowing cognitive decline in patients with mild to moderate AD, large-scale clinical trials assessing cognitive outcomes following NSAIDs administration have been disappointing. Double-blind, randomized, placebo-controlled trials using nonselective NSAIDs and COX-2 specific inhibitors have shown no significant effect on cognitive performance in AD patients. Furthermore, four years of rofecoxib (COX-2-specific inhibitor) treatment in patients demonstrating.

Mild cognitive impairment did not delay the onset of AD. These recent studies from larger populations confirm previous studies incorporating COX-2 inhibitors in smaller subject groups or for shorter duration, suggesting that NSAIDs treatment is ineffectual once memory decline and associated pathology have already developed.

To determine if COX inhibition was effective as a prevention strategy, the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) was designed as the first primary prevention trial to assess the association between NSAIDs and AD incidence, enrolling more than 2,500 cognitively normal elderly patients seventy years or older with one first-degree relative exhibiting dementia. Subjects were randomly administered naproxen sodium (non-specific COX-inhibitor), celecoxib (COX-2-specific inhibitor) or a placebo. Cognitive assessment during 1–3.5 years of treatment did not find a protective impact of celecoxib with respect to AD incidence nor cognitive performance. In fact, the study indicated a cognitive deficit associated with naproxen treatment. Needless to say, these results were disappointing.

The emphasis of COX-2-dependent neuroinflammation in AD has been assumed based on the constitutive and induced expression profiles of COX-1 and COX-2, respectively, in peripheral tissue. However, COX-2 is abundant in post-synaptic dendrites of forebrain neurons in normal brain with COX-2-dependent PGE2 participating in long-term potentiation (LTP) and long-term depression of the hippocampus, a region critical for learning and memory. Observation that COX-2 inhibition leads to cognitive deficits in normal young rodents, implies that constitutive COX-2 activity is necessary for normal neural function. Thus, selective inhibition of pathology-induced COX-2 in neurons and astrocytes may also

compromise activity necessary for normal cognitive function, leading to inconclusive behavioral assessment in studies of dementia.

In contrast, COX-1 is expressed at low levels in resting microglia and induced during inflammatory conditions, lending towards its consideration as a substantial contributor to neuroinflammatory conditions. The relative success of clinical trials using the COX-1-preferential inhibitor indomethacin recent epidemiological studies showing protective effects of aspirin and ibuprofen on cognitive decline, laboratory studies with AD-related transgenic mice treated with ibuprofen or minocycline (tetracycline antibiotic shown to inhibit microglia)and evidence that COX-1 is specifically induced during experimental chronic neuroinflammation, may indicate the benefit of directly attenuating COX-1 activity and microglial activation. Yet, possible thresholds should be taken into account as heavy NSAIDs use may increase risk for dementia and AD. Future pre-clinical studies will benefit from re-visiting the potential value of non-selective NSAIDs treatment and dose, with co-administration of proton pump inhibitors to block NSAIDs-related gastric ulcer disease, to characterize the physiological landscape that precedes and contributes to AD risk and pathology onset.

A final consideration in targeting future investigation is to recognize pre-existing conditions and genetic predispositions in subject populations. For example, in addition to timeframe of NSAIDs exposure, it would be valuable to examine the potential impact of existing peripheral inflammatory conditions that prompted NSAIDs use in the original AD epidemiological cohorts examined relative to the strict selection criteria required for inclusion into the ADAPT trial. Furthermore, NSAIDs therapy may have an impact on AD progression in a subset of at-risk population. Recently, studies have analyzed that a protective effect of NSAIDs was attributed to those subjects having the apolipoprotein E epsilon4 allele (APOE 4). APOE 4 is a genetic risk factor for AD with carriers of two or more alleles having an increased risk of developing AD. As APOE encourages proteolysis of Aβ, future clinical studies may benefit from inclusion of APOE 4 carriers to determine the interaction between genetic predisposition and NSAIDs mechanism of action in AD diagnosis.[2]

13. NASAL DRUG DELIVERY

Nasal drug delivery is a useful delivery method for drugs that are active in lowdoses and show no minimal oral bioavailability. The nasal route circumvents hepaticfirst pass elimination associated with the oral delivery: it is easily accessible andsuitable for self-

medication. Currently, Towclasses of nasally delivered therapeuticsare on the market. The first one comprises low molecular weight and hydrophobicdrugs for the treatment of the nasal mucosa and sinus, including decongestants, topical steroids, antibiotics and other(OTC) products.

The second class encompasses a few drugs, which have sufficient nasalabsorption for displaying systemic effects. Important candidates are the compounds, generally administered by injection and hardly absorbed after oral administration, dueto their instability in gastrointestinal tract, poor absorption properties, and their rapid and extensive biotransformation. Therefore, nasal delivery is promisingalternative route for the administration of peptides and protein drugs in particular.

13.1 ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM

1. Many drugs when given per orally or deep rectally undergo first pass elimination which is the biotransformation of the drug in the gut lumen prior to absorption and in theintestinal epithelium and/or liver after permeation of the intestinal mucosa (pre-systematic) but before entering systemic circulation. For such compounds g.i.t. is poorchoice for administration and nasal route is one of the alternatives.
2. Drugs possessing poor stability in g.i.t. fluids are given by nasal route.
3. Polar compounds exhibiting poor oral absorption may be particularly suited forthis route of delivery.
4. Provides a suitable route of administration for drugs such as peptides orproteins, which are destroyed by the gastrointestinal fluidsand not capable ofbeing adequately absorbed into the systemic circulation following oral.

13.2 LIMITATIONS OF NASAL DRUG DELIVERY SYSTEM

1. There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
2. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
3. The common cold or any pathological conditions involving Muco-cilliary dysfunction, can greatly affect the rate of nasal. Clearance and subsequently the therapeutic efficacy of the drug administered nasally.
4. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

14. Morphology and physiology of the nose

The basic functions of the nose are heating and humidification of inspired air before it reaches the lungs, olfaction, resonance, filtration of particles, mucociliary clearance, and antimicrobial, antiviral and immunological activities. The anatomy of the nose and functions of the epithelial cells at the different regions of the nasal cavity are such that these functions are performedoptimally. The olfactory region situated above the superior nasal turbinate possesses specialized ciliated olfactory nerve cells for smell perception. The central axon of these nerve cells passthrough the cribriform plate of the ethmoid and into the olfactory bulb. The total surface areaofthe olfactory epithelium is 200-400 mm. The nasal vestibule, opening to theoutsideenvironment, possesses numerous nasal that filter large air borne particle. The epithelial cells in this region are stratified, squamous and karatinised withsebaceous gland. Due to its nature, the nasal vestibule is very resistant to dehydrationand can withstand against noxious substances of the environment. On the other hand, permeation of substances through it is very limited. As a result, it is not the preferredsite for drug administration and absorption. The intermediate regionbetween the nasalvestibule and nasal conchae is the atrium. This is a transitional epitheliumregionwith stratified, squamous cells anteriorly and pseudostratified columnar epitheliumwithmicrovilli, posteriorly. Pseudostratified columnar epithelial cells interspersedwith goblet cells cover the respiratory region, and also present are seromucus ducts, the opening of subepithelial seromucus glands. Furthermore, many of these cellspossess actively beating cilia with microvilli. Each ciliated cells containsapproximately 100 cilia, and both ciliated and non ciliated possess approximately 300each. Also present are non-ciliated cells and basal cells. The basal cellssubsequently differentiate to form other epithelial cell types and also believed to helpthecolumnar cells adhere to the basement membrane. collectively, the epitheliumand lamina propria are called respiratory mucus membrance of respiratory mucosa. The respiratory mucosa is the region where drug absorption is optimal. A thin sheet of Mucus produced from the seromucus glands and goblet cells covers the nasalturbinate and the atrium.[2]

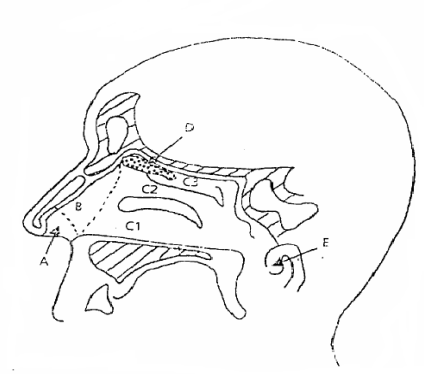

Figure 5: Saggital section of the nasal cavity showing the nasal vestibule (A), atrium (B), respiratory area: inferior turbinate (C1), middle turbinate (C2) and superior turbinate (C3), the olfactory region (D), and nasopharynx (E).

15. ENHANCEMENT OF NASAL DRUG ABSORPTION

Several methods have been used to facilitate the nasal absorption of drugs.

1. Structural modification:-The chemical modification of drug molecule has been commonly used tomodify the physicochemical properties of a drug and could also be utilized toimprove the nasal absorption of drug.

2. Salt or ester formation the drug could be converted to form a salt or ester for a better trans nasal permeability. For example, nasal absorption could be improved significantly by forming a salt with increased solubility in nasal fluid or ester with the enhanced uptake by nasal epithelium.

3. Formulation design Proper selection of pharmaceutical excipients in development of nasalformulation could enhance the formulation stability and/or the nasalbioavailability of drug.

4. Surfactant Incorporation of proper surfactants into nasal dosage forms could modify thepermeability of nasal membrane, which may facilitate the nasal absorption ofdrugs.

16. FACTORS INFLUENCING NASAL DRUG ABSORPTION

The rate and extent of nasal absorption of a drug is dependent uponlipohilicity, envoirnment pH, mucus secreation, etc.

Lipophilicity

The rate and extent of absorption of drug across biological membrane areoften influenced by its lipophilicity. The effect of lipophilicity on the extentof nasal absorption was studied using

series of barbiturates at pH 6, at which barbiturates (pKa=7.6) exists entirely in the non-ionized form.

Environmental pH

The environmental pH plays an important role in the efficiency of nasal drug absorption. Studies of several small water-soluble compounds such as benzoic acid, salicylic acid, and alkaloid acid show that their nasal absorption in rat occurred to the greatest extent at those pH values where these compounds are in the non-ionized form. However, at pH values where these compounds are partially ionized, substantial absorption was found. This means that the non-ionized lipophilic form crosses thenasal epithelial barrier via transcellular route, whereas the more lipophilic ionized form passes through the aqueous Paracellular route.

Table 3: Pathways for nasal absorption.

SUBSTANCE	POSSIBLE PATHWAYS
Naproxen	Nasal mucus membrane- CSF and serum(detected within 15 minutes afteradministration)
Indomethacin	Nasal membrane-CSF (Within 1 minute)
Celecoxib	Nasal membrane- olfactory dendritesnervoussystem supporting cell in olfactorymucosa – submucosal blood vascularsystemCSF(within 1 minute)
Rufecoxib	Dissolved in nasal mucus and thenabsorbed as true solution
Distilled Water	Nasopharynx-cervical lymph.
Chloride salt	Nasal membrane- blood circulation.

The process of transport across the nasal membrane involves either the diffusion of drug molecules through the pores in the nasal mucosa or participation of some non-passivepathways before they reach the blood stream. In addition, the olfactoryepithelium is known tobe a portal for substance to enter the central nervous system(CNS) and the peripheral circulation. However, the mechanism of transport stillremains unknown.[6]

17. SOME NASAL NSAIDs PREPARATION

There are several preparation of nasal spray of NSAIDs that are used now-a-days. Few of them are listed below with their indication for use and limitation of use. For example, SPRIX, DICLOMAX, etc.

17.1 SPRIX (ketorolac tromethamine)

SPRIX is indicated in adult patients for the short term (up to 5 days) management of moderate to severe pain that requires analgesia at the opioid level.

Limitation of use:- Not use for pediatric patients less than 2years of age.

Its nasal preparation gives the 15.75 mg per spray.

Figure 5: Sprix Nasal Spray.

Figure 6: Diclomax (Diclofenac Sodium Spray).

17.2 DICLOMAX (Diclofenac Sodium Spray)

Diclofenac Sodium Spray provide in 0.5mg/dose, 160doses/bottle, 400doses/bottle with specification under BP, USP. Its packing available in one bottle/box. It contains the active substance diclofenac sodium, which belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs). It is used to relieve the acute pain and swelling affecting small or medium-sized joints and surrounding tissues.

18. CONCLUSION

The scientific community has reached a new stage of nasal drug delivery. The nasal drug delivery is a promising alternative to injectables route of administration. It is very likely that in the near future more drugs will come in the market intended for systemic absorption in the

form of nasal formulation. Several formulation factors will influence the development of a drug with a drug delivery system. On a longer term, novel nasal products for treatment of long illnesses such as diabetes, growth deficiency, osteoporosis, fertility treatment and endometriosis are also expected to bemarketed.

The bioavailability of nasal drug products is one of the major challenges for pharmaceutical companies to bring their product in market. The circumstances, which do not favor clinical applicability of nasal drug product is the lack of enough basic research in the area of nasal drug delivery. In contrast; pharmaceutical companies are investing a huge amount of money in the development of nasal drug products because of growing demand of nasal drug products in global pharmaceutical market. This research environment willlead to serious of adverse effects in the society in future. To avoid such backdrops, biomedical scientists, formulation researchers, pharmaceutical companies, funding agencies, and government along with regulatory bodies should pay attention to basic research in nasal drug delivery such as nasal pathophysiology, invention of new excipients to improve the nasal bioavailability, drug delivery devices, toxicodynamic studies of drugs and excipients and in vitro methods for nasal drug metabolism and bioavailability.

Thus, it was novel findings that using nasal NSAIDs in Alzheimer's disease for prevention or curing purposes. As it was available easily or in cost effective manner. So, it was very useful pharmaceutical agents in such type of severe disease with the ease of patient's compatibility and co-operation.

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