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Review article

Nose-to-brain drug delivery: An update on clinical challenges and progress towards approval of anti-Alzheimer drugs

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ABSTRACT

According to the Alzheimer Association Report (2017), Alzheimer's disease (AD) is the 6th primary cause of death in the USA, which affects nearly 5.5 million people. In the year 2017 itself, the cost of AD treatment in the USA has been reported to rise to $259 billion. This statistic shows the severity of the disease in the USA which is very much similar across the globe. On the other hand, the treatment remains limited to a few conventional oral medications (approved by FDA). These are mainly acting superficially from mild to the moderate AD. The therapeutic efficacy of the drug is not only affected by its reduced concentration in the brain owing to the existence of blood-brain-barrier (BBB) but also due to its low brain permeability. In this context, the intranasal (IN) route of drug administration has emerged as an alternative route over the systemic (oral and parenteral) drug delivery to the brain. The delivery of the drug *via* an IN route offers various advantages over systemic drug delivery system, as it directly delivers the drug into the brain *via* olfactory route. Presence of drug in the olfactory bulb, in turn, increases the drug bioavailability in the brain and reduces the drug degradation as well as wastage of the drug through` systemic clearance. However, there is also some limitation associated with IN like poor drug permeation through the nasal mucosa and mucociliary clearance. The delivery system various through novel strategies (nano drug carrier system, colloidal carriers, mucoadhesive devices, controlled delivery system, pro-drug, *etc.*) are adapted to overcome the above-stated limitations. Although, after all, such successful research claims, very few of the nose-to-brain drug delivery of anti-AD drugs have gained market approval due to lack of sufficient clinical evidence. Onzetra Xsail® is one such marketed preparations approved for IN delivery used for the treatment of a brain disorder; migraine. In the field of patents also, no work is found which could present sufficient experimental findings to support its clinical safety profile. It also underlines the fact that majority of work related to the nose-to-brain delivery of anti-AD drugs is limited only up to preclinical studies. In this review article, we have discussed the latest works on various novel formulations loaded with various anti-Alzheimer agents. These agents include galantamine, deferoxamine, tacrine, tarenflurbil, rivastigmine, risperidone, curcumin, quercetin, piperine, insulin, *etc*. and various peptides towards the development of a promising IN drug delivery system for the treatment of AD. Through this review article, we want to drag the attention of the researchers working in this field towards the challenges and hurdles of practical applicability IN delivery of anti-AD drugs. Moreover, the attention towards the clinical studies will ease the approval process for the administration of anti-Alzheimer drugs *via* IN route.

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1. Introduction

The Alzheimer Disease (AD)[1] is a significant cause of dementia [1–3] or memory loss throughout the world that mainly affects older adults, but in modern lifestyle, it seems to touch people at an early age which is known as younger stage AD [4,5]. Alzheimer is a CNS[2] disorder characterized by progressive deterioration of neurons resulting in loss of cognitive behavior, memory impairment, and disturbance in a daily routine activity like brushing, bathing, eating, drinking, communication, reading, writing, *etc.* overall disturbing the thinking ability and causes mental illness thereof [4]. Different studies and statistics show that around 47 million people worldwide have dementia among which 37 million are having AD [6]. The Alzheimer Association report (2017) states that in the USA approximately 5.5 million people live with Alzheimer originated dementia and is considered as a 6th leading cause of death of older adults in the USA. This ratio is assumed to get doubled in every twenty years and expected to reach up to 131 million by 2050 throughout the world. The average expense, the treatment is too high and also makes the procedure unaffordable for a person with middle economic status. Only in the USA, the total cost of AD treatment is approximately $259 billion which expected to rise by 1 trillion by 2050. The statistics indicate that in last 15 years, AD increases as a more significant cause of morality even in comparison with other lethal conditions like heart disease, cancer, and many more. The death rate due to heart diseases falls up to 14% while increases by 89% due to Alzheimer's in the USA. Although, India falls in the list of countries with the lowest rate of Alzheimer incidences (0.46) as compared to the USA (45.58). In India, the figure is about 4.1 million elderly peoples with dementia. However, after that, we must be gravely concerned about the proper management strategies of this epidemic mental disorder to avoid as well as prevent the incidences of future [7]. The term dementia and Alzheimer distinctly different from each other's as dementia is only considered as the loss of memory while Alzheimer is a group of symptoms like memory loss, thinking and behavioral disability, cognitive memory impairment, mood swings, difficulty in communication, reading, writing and other daily activities [8]. Hence, it does not only affect the person suffering from but also the family of the patient. The exact reason behind the disease is still not known, but it was supposed to be related to the genetic factors, food habits, lifestyle changes, mental stress, *etc.* [9]. The histopathology behind is multifactorial disorder regulated by some different pathophysiologies. The primary hypothesis behind AD includes a) Amyloid cascade hypothesis; b) Tau hypothesis; c) Cholinergic hypothesis, d) Excitotoxicity hypothesis, e) Mitochondrial cascade hypothesis, f) other reasons (like genetic factors, inflammatory responses, free radical or oxidative stress, nitric oxide or toxins, environmental factors, *etc.*); [10–12] shown in Fig. 1.

The drugs used for the treatment of AD remain divided into two categories, one is symptomatic (cures the symptoms of disease) like rivastigmine, galantamine, donepezil (AChE[3] inhibitors) while the other one remains targeted (act on the specific site or physiological factor of the AD) [13]. Although, the availability of such promising drug molecules does not assure the treatment of AD till date. This uncertainty is because of the complicated structure of the brain, especially the existence of BBB[4] which does not allow the entry of most of the outside substances to the brain. Almost all the drug moieties suffer from low bioavailability (in the brain) due to less permeability across the BBB [14–17]. Table 1 shows the mechanism of drug action and strategies adopted to improve their efficacy.

2. Intranasal drug delivery

Most of the available treatments of the AD and other CNS disorders utilize the peripheral route of drug administration (Oral and parenteral administration). This kind of attempt reduces the efficacy and potency of the drug therapy. The major drawback of the peripheral administration of the drug is the limited accessibility of the drug molecules or active agents to the brain from the blood [18]. It may be due to the presence of BBB which restrict the entry of almost all the drug molecules, various phytoconstituents, proteins, peptides and other large substances; to protect the brain from any harm [19]. At the same time, the first pass metabolism and enzymatic degradation (oral administration) and systemic clearance (in oral and parenteral route) also significantly reduce the drug bioavailability [20]. Along with this, the plasma protein binding, volume of distribution, delayed delivery to the brain through blood and a peripheral side effect of the systemic drug delivery triggers the hunt for an alternative route that directly delivers the drug to the brain. In this sequence, the intracerebroventricular injection can be an option, but the approach is highly pain invasive. It is only feasible in extreme conditions by highly experienced hands and seems almost irrelevant to use [21]. Among all these complexities of brain drug delivery, IN[5] route come out as a comfortable and convenient approach that bypasses the BBB and deliver the drug directly to the brain from the nasal cavity [22–24]. Various theories and research claims that IN route of brain drug delivery overcome the limitations of systemic drug delivery and fastened the drug delivery process [25–27]. At the same time, it also offers noninvasive and effective treatment of CNS disorders [28–30]. The IN route is already a favorite route of drug administration to the systemic circulation and for topical application, but here we concern about the application of such non-invasive and effective route for direct brain drug delivery [31–33]. William H. Frey II, 1989 discovered the first concept of the intranasal route for the delivery of therapeutically active compounds directly into the CNS [34]. Since then a remarkable study has been done in the nose-to-brain drug delivery system [35]. Initially, the investigation focused on the IN delivery of insulin to the brain for the treatment of AD. Shortly, it was noticed that along with insulin, various other proteins and peptides remain available for the efficient delivery to the brain *via* the IN route. Also, numerous investigations based on different peptides and proteins (like wheat germ agglutinin, insulin, melanocortin, oxytocin, nerve growth factor (NGF), *etc.*) support/confirm the hypothesis of direct nose-to-brain drug delivery. Nevertheless, there are also some contradictions in the direct passage of drug from the nasal cavity to the brain. A group of scientist does not observe any traces of estradiol in the CSF after nasal administration [36] while another group of scientists found significant drug targeting of the same molecule after IN administration as compared to the intravenous route [37]. Similar contradictory data remain perceived with the IN administration of vitamin-B12 and melatonin. These contrast data indicates the need for a precise experimental methodology for nose-to-brain drug delivery. The successful development of IN drug delivery to the brain needs a proper understanding of the mechanism of drug transport, pathophysiology of the disease, anatomy of the brain and various formulation as well as experimental parameters [38].

3. Mechanism of nose-to-brain drug delivery

The illustration is shown in the Fig. 2 which depicts the general mechanism of drug transfer from the nasal cavity to the brain. When the drug molecules entered into the nasal cavity supposed to reach the brain by two primary pathways a) neuronal pathway (major pathway) and b) through systemic circulation, by crossing the BBB (minor pathway) (Fig. 2). The nasal cavity, divided into three regions (i) the

[1] Alzheimer disease.
[2] Central nervous system.
[3] Acetylcholinesterase.
[4] Blood-Brain-Barrier.
[5] Intranasal.