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Intranasal insulin therapy in the treatment of alzheimer's disease – A narrative review

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ABSTRACT

The administration of intranasal insulin improves symptoms related to Alzheimer's disease. The research was conducted through a hypothesis-based review, such as, PubMed, DynaMed, and EBSCOhost. The articles published between 2011 and 2020 were included. The studies included randomized controlled trials and cohort studies. The study populations included participants associated with cognitive-related conditions. The group of humans and animal models were also considered. All ten articles showed how the administration of intranasal insulin can improve the symptoms related to Alzheimer's disease. However, these findings varied on the level of dose used, the duration of the treatment and the type of insulin formulations used. Future studies can consider to provide a more homogenous group of study population, cognitive-related activities to observe, and duration of the administration in order to provide a more credible result.

1. Introduction

The start of recognizing insulin as a vital regulator of energy metabolism started in the early 20^{th} century when it was discovered as a treatment for diabetes. By increasing the uptake of the cell glucose, the primary role of the insulin is to clear the blood glucose. For several years, the study insulin-interceded effects in the central nervous system have mainly been disregarded. However, it changed when several studies in the middle of 1980s were published and described insulin receptors in the central nervous system and how it may play a vital role in neurotransmission in the brain and glucose uptake. Leading the way for more advanced research became possible because of these studies, and eventually ratifying that insulin is a significant hormone for the function of the central nervous system (Avgerinos et al., 2018). [1–6]

The studies were able to detect in several brain regions proteins that were contributing to the transmission of the insulin signal. This included areas that are affected by the famous Alzheimer's disease (AD), thereby including the temporal lobes and hippocampus. This was due to how insulin signaling is reduced in postmortem brain tissue from AD patients and due to how it is recognized that insulin positively provides influence on cellular developments such as survival and growth (Morris & Burns, 2012; Avgerinos et al., 2018).

Considering that AD is the most common type of dementia, it is also posing a higher threat to the public health. The 2015 World Alzheimer Report for instance showed that there are 46.8 million people globally who were living with dementia. By 2030, this is anticipated to reach the number of 74.7 million and to as many as 131 million by the year 2050. (Huang & Mucke, 2012).

What is perceived to be one of the etiologies for irregular AD, defective insulin signaling has been observed in the brain of AD patients (Ferreira et al., 2014). Insulin signaling

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controls the neuronal and glial roles in the central nervous system such as the synaptic plasticity and synaptogenesis through gene expression, cognition and energy homeostasis. According to numerous studies, AD patients have flawed or malfunctioning insulin receptor (IR) expression as well as IR binding. This also includes the reduced IR substrate-1 and IR substrate-2 expression, along with the augmented levels of incapacitated serine-phosphorylated IR substrate-1 (Talbot et al., 2012).[7–9]

An effective approach that enables neurotrophins or therapeutic agents to bypass the blood-brain barrier and openly reach the brain defines the intranasal insulin administration. This process is observed to avoid side effects that are caused by universal delivery.

For several years, this has also been performed in animal models such as mice or rats. The studies that were conducted in animals showed that peptide carriers near the olfactory bulb quickly transport a few numbers of peptides, which includes insulin, into the cerebrospinal fluid, from which these elements will further reach the brain cells. This hypothesis-based review aims to provide a support on how a collective form of reviewing the findings of past studies have already possibly provided a small solution to a current and possibly future public health issue.[10–15]

2. Materials and Methods

In order to effectively conduct a literature review, credible databases were selected that includes PubMed, Research Gate, DynaMed Plus and EBSCOhost. The inclusion criteria for the research articles would be from year 2011 up to the present. The researcher included studies which were (1) randomized controlled trial; (2) randomized double-blind placebo controlled triad; (3) cohort study; and/or (4) in vivo animal trial. As for the participants, it can either be humans or animal models as long as it covers an examination that are specifically covering or related to the (5) mechanism of insulin signaling; (6) Alzheimer's disease; (7) intranasal insulin; (8) dementia; and/or (9) cognitive impairment. The exclusion criteria for this study includes all articles that were published before 2011.

The articles were gathered based on the different keywords used in the search. There were 160 articles in total but only ten were used for this study. The next step was the screening of the articles, which involved removing the duplications. The articles were then reduced into a lesser number by screening its title and abstract and only choosing those that consist of the keywords to be used for the study, namely "intranasal insulin", "insulin signaling", "Alzheimer's disease", "dementia", and "cognitive impairment". This then led to the eligibility assessment, which resulted into only selecting 12 articles. Further assessment for its eligibility involves identifying the type of research method used. There were two non-RCTs and one that provided insufficient data, thus resulting into having 10 articles as the final number of studies to be reviewed. The figure below gives the keywords the definition that will serve as a basis on how the study should be understood and started with.

Intranasal Insulin	A type of insulin administration that is conducted through a spraying device and sprayed on the nasal cavity, aiming to improve brain insulin.
Insulin Signaling	A pathway and the entirety of every protein covered in the activity of insulin in the body.
Alzheimer's Disease	A progressive and permanent brain disorder that slowly damages thinking and memory skills and, sooner or later, affecting as well the capacity to perform the simplest errands.
Dementia	A general term used to define language, problem-solving, and memory loss; one of its most common cause is the Alzheimer's disease.
Cognitive Impairment	A term that generally presents a state of trouble making sense or understanding, loss of attentiveness or memory, confusion, difficulty recognizing things, people, or places, or mood changes.

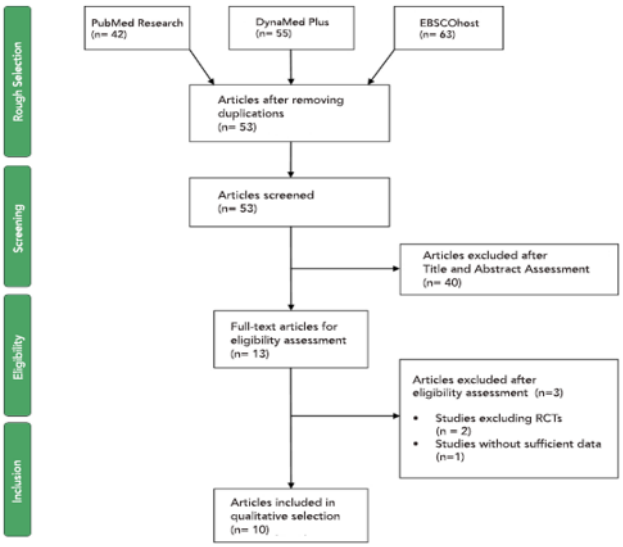

Fig. 1: Flow chart of article selection

Table 1: Evidencetable for the systematically reviewed articles

First Author	Study Design (Level of Evidence)	Study Population	Therapy	Outcome
Maimaiti, S Feb 2015	Cohort (4)	Young male F344 (3 months old), aged male F344 (21 months old), and young male Sprague-Dawley rats (2–6 months) old)	Short acting Insulin Lispro (Humalog) and Long acting Insulin Determir (Levemir)	Low dose insulin improved memory recall in aged animals. Performance of aged animal were similar to that seen in younger animal.
Craft, S Jan 2012	Randomized, Double-Blind, Placebo-Controlled Triad (1)	64 adults with amnestic mild cognitive impairment and 40 adults with AD.	Placebo, 20 IU of Insulin, 40 IU of Insulin	Treatment with 20IU of insulin improved delayed memory. Both doses of Insulin preserved caregiver-rated functional ability and general cognition. Placebo assigned participants showed decreased fludeoxyglucose.
Kullman, S Jan 2018	Randomized Controlled Trial (1)	Nine healthy men, 20 to 26 Kg/m2; age 23 to 30 years.	Placebo, 40 U, 80 U and 160 U Insulin Spray	Intranasal insulin dose modulated regional brain activity. The strongest effects were seen after administration of 160 U of nasal insulin, the highest dose administered in this study. However, an excess of insulin in blood was detected, resulting in a transient increase in circulating insulin.
Anderson, K Apr 2016	In Vivo Animal Trial (6)	Young and Aged F344 rats.	Intranasal Apidra (Zinc Free Insulin Formulation)	In young or aged F344 rats neither acute nor chronic Apidra improved memory recall. However, chronic Apidra was able to offset reduced CBF with aging. Insulin Apidra caused significant reduction in markers of neuronal integrity.
Guo, Z Apr 2017	In Vivo Animal Trial (6)	ICV-STZ rats	2/U daily of Intranasal Insulin	Six weeks of Intranasal Insulin therapy, notably improved cognitive function, microglial activation and neurogenesis in ICV-STZ rats. Also reduced drastically the level of tau hyperphosphorylation.
Claxton, A Sep 2014	Randomized Controlled Trial (1)	60 adults with mild cognitive impairment or mild to moderate AD	Placebo, 20 IU Insulin Determir, 40 IU Insulin Determir. Everything administered nasally with a special nasal drug delivery device for 21 days.	Improved memory was seen in the 40 IU group compared with placebo, especially for APOE-4 carriers. However, worsening was observed for non-carriers. Significant treatment effects were also apparent for verbal working memory visuospatial working memory. Lastly, daily therapy and administration with 40 IU insulin detemir enhanced cognition for adults with AD or MCI.

Continued on next page

Table 1 continued

Craft, S Apr 2017	Randomized, double-blind, placebo-controlled trial(1)	36 adults with mild cognitive impairment or mild to moderate AD	Placebo, 40 IU of regular insulin, 40 IU of insulin Determir daily for 4 months.	Memory improvement was observed after two and four months of treatment in group treated with 40 IU of regular insulin in comparison with placebo. On the other hand, no significant effects were observed for Determir assigned group compared with placebo.
Novak, VC Mar 2014	Randomized, double-blind, placebo-controlled trial(1)	15 DM patients and 14 control subjects.	Single dose of 40IU of Intranasal Insulin or Saline	Intranasal insulin improved cognitive function in group with DM without affecting systemic glucose levels. It is believed that the cognitive improvement is due to vasoreactivity mechanisms, but further studies are required.
Mao, Y Jul 2016	In Vivo Animal Trial(6)	4.5 months homozygous APPswe/PS1dE9 (APP/PS1) double-transgenic mice harboring human APPswe (Swedish mutations K594N/M595L)	Intranasal Insulin for 6 weeks	Insulin treatment for 6 weeks effectively reduced anxiety-related behaviors and ameliorate cognitive impairments, impaired brain insulin signaling, and neurogenesis, and substantially decrease brain AB Level and AB plaques. A marked reduction in APO-E protein in young adult APP/PS1 mice were also observed. These findings proposed that intranasal insulin can improve cognition, Enhance insulin signaling, alleviate the AB Pathology, and benefit neurogenesis.
Stein, M.S. et al. Apr 2011	Randomized Controlled trial(1)	63 individuals aged 60 and above; more than half of the population has mild-moderate disease	Low dose of vitamin D (1000IU per day) for 8 weeks. Followed by random addition of high-dose D/placebo for another 8 weeks. Followed by nasal insulin with 60 IU qid/placebo for 2 days.	Vitamin D gave no benefit for disability or cognition from adding the said doses on different stages. The same with how it improved the benefit of insulin after being given acutely or over 2 days (48 hours). However, researchers did not reject the possibility that the capacity of high-dose vitamin D has been removed by the protective capacity of the low-dose vitamin D.

3. Results

Ten articles were eventually considered eligible, which includes randomized controlled trial (n=3), in vivo animal trial (n=3) randomized double-blind placebo-controlled trial (n=3), and a cohort study (n=1). The participants varied from young to elderly humans and young to aged rats or mice. Every study was designed to determine whether intranasal insulin can improve the cognitive ability of the participants.

In their study, Guo et al. (2017) aimed to treat intracerebroventricular streptozotocin-injected (ICV-STZ) rats. While Mao et al. (2016) used transgenic mouse models that are widely used to test Alzheimer's disease. For six consecutive weeks, the researchers delivered 2 U of insulin each day, which was then followed by studying the subjects' cognitive function with the MWM test and biochemical changes through Western blotting. Guo et al. (2017) gave focus on how the intranasal insulin treatment can attenuate the level of tau hyperphosphorylation and improve microglial activation. The study showed that the treatment can improve neurogenesis in the animal models.[16–18]

Their findings also showed that the six-week treatment reduced tau phosphorylation in the brains of the rats. In this study, the role of PP2A, a major tau phosphatase found in the human brain, was highlighted and how its activity is radically decreased in a brain that suffers from AD. For this reason, the researchers also studied whether PP2A is also part of the inhibitory effect of insulin on tau hyperphosphorylation in the brains of the ICV-STZ rats. The findings showed that PP2A might not be considered as part of the hyperphosphorylation of tau activated by STZ. Moreover, the researchers also stated that the reduced tau phosphorylation in intranasal insulin treated rats might not be considered as the outcome of the improved activity of PP2A.

In the study of Anderson et al. (2016), the researchers specifically directed a group of in vivo experiments in order to examine the impact of intranasal Apidra on the brain of both young and aged F344 rats. Apidra is defined as a zinc-free insulin formulation. Apidra dose was selected to 10 IU per day.

The overall findings of the study showed that neither chronic nor acute insulin (IN) Apidra was able to improve memory or learning on the spatial MWM. The 24-hour recall on the MWM test in aged F344 rats showed that it did not improve memory of learning of the platform location. The aged rats continued to show poor performance during the 24 hours of the test. Overall, Apidra was not successful in improving memory recall on aged rates. (Anderson et al. 2016).

In another study, Maimaiti et al. (2015) conducted cohort research, which involved young male, aged male, and young male Sprague-Dawley rats. The researchers used the short acting Insulin Lispro called Humalog and a long-acting Insulin Detemir or Levemir. The young male F344 rats were 3 months old, 21 months old for the aged male F344, and 2 to 6 months old for the young male Sprague-Dawley rats. The young male rats were excluded from receiving insulin treatment and were only used to help measure the impact of the formulation on the aged rats' memory function.

Maimaiti et al. (2015) compared the actions of Humalog to zinc and artificial cerebro-spinal fluid (ACSF). In the existence of zinc from the extracellular recordings, it revealed that there was little, if any, effects on extra-cellular postsynaptic potentials given by the insulin. As for the intracellular recordings achieved from the similar group of subjects, the Ca2+-dependent after hyperpolarization (AHP) has shown that it was sensitive to treatment with insulin or zinc. The findings then suggest that there is a constituent of the insulin effect on the AHP could relatively be interceded by zinc that can be found in the insulin formulation.

In the study of Craft et al. (2012), 64 adults with amnestic mild cognitive impairment and 40 adults with AD were selected as patients who will receive an intranasal insulin treatment. This allowed the researchers to test whether the treatment produces an effect on cerebral glucose metabolism and cerebrospinal fluid biomarkers of the participants with distinct diagnosis. For a duration of four months, 30 participants received placebo, 36 for 20 IU of insulin, and 38 participants for 40 IU of insulin. For the primary measures used by the researchers, involved delayed story recall score as well as the Dementia Severity Rating Scale score. The Alzheimer Disease's Assessment Scale-cognitive subscale (ADAS-cog) score and the Alzheimer's Disease Cooperative Study-activities of daily living (ADCS-ADL) scale were used for the secondary measures.

The group that was given 20 IU of insulin revealed an enhanced delayed story recall unlike the placebo group. As for the group that were given 40 IU of insulin, there was no improvement that was observed. On the secondary part of the analysis, the ADAS-cog showed significant effects wherein both insulin groups showed less reduction in cognition in contrast with the placebo group on the ADAS-cog (P =.04 for the 20-IU dose insulin group and P=.002 for the 40-IU dose insulin group).

The study of Novak et al. (2014) focused on older adults with type 2 diabetes mellitus (DM). It used 40-IU dose of insulin. The measurements focused on vasodilatation, regional perfusion to hypercapnia with 3-Tesla MRI and a neuropsychological assessment. The findings showed that intranasal insulin improved cognitive function in group with DM without affecting their systemic glucose levels. It is believed that the cognitive improvement is due to vasoreactivity mechanisms.

This study showed that the administration of intranasal insulin seems to be safe when given to older adults with type 2 DM and how it does not provide an impact on

systemic glucose control. Moreover, it may also offer acute improvements in the older non-demented DM and non-DM patients' cognitive function. Accordingly, a possible mechanism of acute intranasal-insulin developments in cognitive performance may be observed in the activation of anterior brain regions that control visuospatial memory. This has been suggested by the observed connection between vasodilation and cognitive improvement in the anterior brain circulation.

Craft et al. (2017). Study comprised 36 adults who were diagnosed with mild-to-moderate AD or amnestic mild cognitive impairment (MCI). Three groups of participants received 40 IU of insulin detemir, placebo, and 40 IU of regular insulin daily for an exact four-month-treatment. The aim of this study was to determine whether a long-term administration of the treatments could provide a positive effect on the participants' daily functioning, AD biomarkers and cognition.

Memory improvement was observed after two and four months of treatment in group treated with 40 IU of regular insulin in comparison with placebo. On the other hand, no significant effects were observed for Determir assigned group compared with placebo.

4. Discussion

Majority of the studies gathered and selected for this review supported the hypothesis that the administration of intranasal insulin can improve the symptoms related to Alzheimer's disease, thus allowing the treatment to provide an effective way of reducing the negative impact of the disease. In this review, we found indication that intranasal insulin may provide a beneficial effect on patients that receive longer duration of treatment of insulin formulations that are found to be of low- or moderate-level of dose provided. Another factor to consider is the age of the participants who receive it, but only for the in vivo animal trial or those studies that utilized animals as the subjects for the experiments. Lastly, the effect of the different types of insulin formulations have also been observed to carry out different levels of effects considering that the studies have creatively determined how to examine its effect on the cognition, memory recall capacity, and/or the existence of AD and other related issues.

The difference of doses provided for the participants showed a difference on the impact of the intranasal insulin administration. The study of Maimaiti et al. (2015) conducted a cohort study in which a low dose insulin showed an improvement in memory recall in both the young and aged animals. The low dose of insulin in this study amounted to 0.0715 IU each day for one rat. The researchers in this study considered the brain weight of the rats who will receive the insulin treatment, thus seeing a lower dose of the treatment.

In another study, Kullmann et al. (2018) showed that nasal insulin dose-dependently moderated regional brain activity with the strongest effects after providing 160 U of nasal insulin. However, an excess of insulin in blood was detected, resulting in a transient increase in circulating insulin.

In another study, two different doses were given to the participants wherein 20-IU dose of insulin and 40-IU dose of insulin were provided. The findings showed in its primary outcome measure of delayed story recall that the 20-IU dose of insulin was able to improve the performance of the participants while those that received the 40-IU of dose insulin showed the opposite. Contrary to these findings, both of the doses showed beneficial effects on the co-primary measures, which includes the ADAS-cog and DSRS. In this case, we can link the fact that the insulin-dose response curve for memory is described by a ∩-shaped role wherein the positive effects are perceived at optimal or top levels, while negative or null effects are perceived when the levels are found to be too high or too low (Reger et al., 2008).

The shortest duration given to the treatment was three weeks and accompanied by 20 to 40 IU doses of insulin. This duration of the treatment was considered to by earlier studies to offer preliminary signs of efficacy and safety and that would potentially support further longer-term examination. In fact, utilization the emergence of intranasal insulin as an effective treatment tool for patients with AD has already been observed in several studies (Benedict & Grillo, 2018).

While the study of Claxton et al. (2014) showed an improved memory of the adults with mild cognitive impairment or mild-to-moderate AD after three weeks of insulin treatment, the effects has also shown some negative effects. This may then be considered as a potential topic for another study on how the duration of treatment may have caused the effect especially when compared with other studies that showed more positive effects with a longer duration of treatment imposed. For instance, the six-week intranasal insulin treatment given by Guo et al. (2017) to ICV-STZ rats has shown an improvement on their cognitive function and how it weakened the level of tau hyperphosphorylation, improved neurogenesis and improved microglial activation.

The different types of insulin provided to the subjects also showed an impact on the study's outcome. Although Apidra insulin appears to have not shown any capacity to fight cognitive decline in brain aging, the examination of this particular formulation has been deemed to be valuable in reaching a more higher possibility of finding ways to treat AD and other related diseases. Accordingly, the possible mechanisms of insulin actions that are observed in the brain consist of N-methyl-D-aspartatic acid (NMDA), metabolic, ionic, genomic processes, and alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) that

independently or collectively capable of increasing memory tasks performance. Moreover, this has been found to have slowly given a clearer understanding on how insulin plays a vital role in memory recall and processing both in animal models and humans (Freiherr et al., 2013).

Humalog, a short-acting insulin, has also been found in some of the studies. The way that long-acting insulin provided positive effects, Humalog has also been found the same and this was credited from its amino acid modifications observed in the insulin molecule's β-chain. Humalog, along with Detemir or Levemir, were able to gain access to the brain after its administration and regardless of the structural variations. This was because of how both types of insulin formulations were capable of reversing cognitive deterioration to the same extent in aged animals. However, it is unclear that higher doses of Humalog might not be ineffective, the same way that a higher Levemir dose, even though the same insulin dose produced a quantitatively similar improvement on memory recall in two cohorts of aged animals. Thus, future studies can then use this source to further shed light on the brain's insulin mechanism such as how the deteriorations in the AHP could improve neuronal communication and how it might also be capable of representing a pathway through which long-acting or short-acting insulin formulation may improve memory recall in aged animals.

Although tested in a small number of clinical trials, intranasal insulin is already considered as an innovative treatment for patients with Alzheimer's disease and cognitive impairment. With a highly diversified effect of the different factors involved in the ten selected articles, this hypothesis-based review poses several limitations. The small sample size for some studies have given the researchers a dilemma and a more curious mind on how the effect would be considered to be more credible if there would be a higher number of participants. However, the safety concerns may interject with this category, along with the duration of the administration of the insulin. For this reason, future researchers should also be able to provide a way on how a longer duration of administration can be possible in a sense that it would be accepted as safe and therefore allowing them to observe whether a longer effect of the treatment could also be possible.

Even though there were similar cognitive domains observed in the studies, there were different cognitive tasks observed, which therefore provided a lower level of effective direct comparison and theorization. Furthermore, the doses and types of insulin formulations have also differed between the studies.

5. Conclusion

The current hypothesis-based review studied how intranasal insulin can improve the related symptoms of Alzheimer's disease and therefore allow it to be treated or weakened. The collective evidence reveals that intranasal insulin administration can improve memory delay and/or other cognitive-related activities, both for humans and animal models. The studies differed from its study design, population and therapy or administration, thus showed a higher rate of heterogeneity and possible lack of credibility of the interpreted findings. However, majority of these posed a higher potential for intranasal insulin as an effective tool in treating or preventing AD and other cognitive-related conditions. Several factors are to be considered for future studies in order to provide a much more robust group of evidences on these findings, including as well the prioritization of safety concerns. For clearer results in future studies, accurate selection of populations for a study, a homogenous group of study design, duration of insulin administration, defined cognitive conditions or activities to observe, level of doses and types of insulin formation are needed.

6. Source of Funding

None.

7. Conflict of Interest

None.

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