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Effects of intranasal insulin on cognition in memory-impaired older adults: Modulation by APOE genotype

M.A. Reger[a,b], G.S. Watson[a,b], W.H. Frey II[f,g], L.D. Baker[a,b], B. Cholerton[a,b], M.L. Keeling[a,b], D.A. Belongia[a,b], M.A. Fishel[a,d], S.R. Plymate[a,c], G.D. Schellenberg[a,c,d,e], M.M. Cherrier[a,b], S. Craft[a,b,*]

[a] *Geriatric Research, Education, and Clinical Center, Veterans Affairs Puget Sound Health Care System, 1660 S, Columbian Way, S182-GRECC, Seattle, WA 98108, USA*
[b] *Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA 98195, USA*
[c] *Department of Medicine, University of Washington School of Medicine, Seattle, WA 98195, USA*
[d] *Department of Neurology, University of Washington School of Medicine, Seattle, WA 98195, USA*
[e] *Department of Pharmacology, University of Washington School of Medicine, Seattle, WA 98195, USA*
[f] *Alzheimer's Research Center, Regions Hospital, St. Paul, MN 55101, USA*
[g] *Department of Pharmaceutics, University of Minnesota, Minneapolis, MN 55455, USA*

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Abstract

Raising insulin acutely in the periphery and in brain improves verbal memory. Intranasal insulin administration, which raises insulin acutely in the CNS without raising plasma insulin levels, provides an opportunity to determine whether these effects are mediated by central insulin or peripheral processes. Based on prior research with intravenous insulin, we predicted that the treatment response would differ between subjects with (ε4+) and without (ε4−) the APOE-ε4 allele. On separate mornings, 26 memory-impaired subjects (13 with early Alzheimer's disease and 13 with amnestic mild cognitive impairment) and 35 normal controls each underwent three intranasal treatment conditions consisting of saline (placebo) or insulin (20 or 40 IU). Cognition was tested 15 min post-treatment, and blood was acquired at baseline and 45 min after treatment. Intranasal insulin treatment did not change plasma insulin or glucose levels. Insulin treatment facilitated recall on two measures of verbal memory in memory-impaired ε4− adults. These effects were stronger for memory-impaired ε4− subjects than for memory-impaired ε4+ subjects and normal adults. Unexpectedly, memory-impaired ε4+ subjects showed poorer recall following insulin administration on one test of memory. These findings suggest that intranasal insulin administration may have therapeutic benefit without the risk of peripheral hypoglycemia and provide further evidence for apolipoprotein E (APOE) related differences in insulin metabolism.

Keywords: Cognition; Alzheimer's disease; Diabetes; Memory; Glucose

1. Introduction

Several mechanisms are now recognized through which insulin may influence central nervous system (CNS) functioning. Insulin-sensitive glucose transporters (GLUT4 and 8) are expressed in brain and are co-localized with insulin and insulin receptors in the hippocampus and hypothalamus [1,3,7,18,27,28,32,44,56]. Changes in insulin levels may thus affect physiology in these selective brain regions. Insulin may also modulate long-term potentiation (LTP). For example, insulin influences cell membrane expression of NMDA receptors, which affects the induction of LTP [61]. In addition, insulin modulates CNS concentrations of neurotransmitters, such as acetylcholine and norepinephrine, which influence cognitive function [21,37].

Converging evidence suggests that insulin abnormalities in the CNS play a significant role in some neurodegenerative

* Corresponding author. Tel.: +1 206 277 1156; fax: +1 206 764 2569.
E-mail address: scraft@u.washington.edu (S. Craft).

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diseases, such as AD [15]. We have reported that patients with AD showed lower CSF insulin levels, higher plasma insulin levels, and reduced CSF-to plasma insulin ratios compared to healthy controls [14]. Also, reduced insulin receptor tyrosine kinase activity has been demonstrated in AD brain [23]. Lower levels of brain insulin may occur as a result of the chronic peripheral hyperinsulinemia that has been documented in some patients with AD [12,14,40,48,55]. Peripheral hyperinsulinemia may down-regulate transport of insulin to the brain. For instance, genetically obese hyperinsulinemic Zucker rats showed reduced insulin binding to brain capillaries [60] and reduced hypothalamic insulin levels [25]. Acute administration of insulin may improve memory by supplementing low brain levels or overcoming insulin resistance. In rats, intracerebroventricular insulin administration enhanced memory [50]. In humans, intravenous insulin administration, while maintaining euglycemia, improved verbal memory [9,10,12,13,69]. However, peripherally administered insulin is not a viable treatment option due to risks associated with hypoglycemia.

This risk can be circumvented with an intranasal administration technique in which insulin travels through a nasal pathway to the brain and largely bypasses the periphery [6,22]. A significant number of compounds have been successfully delivered to the brain or CSF following intranasal administration [2,6,20,47,51,57,58,64,65]. For example, insulin-like growth factor-I (IGF-I) has been delivered to the brain following intranasal administration, resulting in reduced infarct volume and improved neurological function [41–43]. In healthy, young adults, intranasal administration of insulin resulted in increased CSF insulin levels within 10 min of administration with peak levels noted within 30 min [6]. CSF insulin levels had not returned to baseline by the end of the 80 min study, while blood glucose and insulin levels did not change. Intranasal insulin administration also induced changes in evoked brain potentials [34] and improved verbal memory in young, healthy adults [4]. The rapid transport of compounds following intranasal administration indicates that the primary pathway is extraneuronal, although an additional olfactory intraneuronal pathway is also possible hours later [65]. Recent evidence supports three extracellular pathways from the nasal cavity to the CNS. Drugs can access the CSF along the olfactory neurons and cribriform plate, or they can enter the CNS parenchyma through channels associated with the olfactory or peripheral trigeminal systems [22,65,66]. These findings suggest that intranasal insulin administration may produce the same memory facilitation as IV insulin, but without the risk for hypoglycemia.

The purpose of the present study was to test the hypothesis that intranasal administration of insulin would improve memory in subjects with AD or amnestic mild cognitive impairment (MCI) without raising plasma insulin. Amnestic MCI is widely believed to represent a prodromal stage of AD with approximately 80% of patients receiving an AD diagnosis within 6 years [52]. Prior studies have demonstrated that the dose of insulin required for memory facilitation may differ according to apolipoprotein E (APOE) genotype [9,11,12,14]. Therefore, we predicted that the treatment response would differ between subjects with (ε4+) and without (ε4−) the APOE-ε4 allele, a genetic risk factor for sporadic AD.

2. Method

2.1. Subjects

This study was approved by the Human Subjects Review Committee of the University of Washington. Written informed consent was obtained from all subjects and from the legal representatives of the subjects with AD. Memory-impaired subjects included those diagnosed with probable AD (NINCDS/ADRDA) [45] or amnestic MCI [53].

There were 35 normal adults (ε2/3 $n = 8$, ε3/3 $n = 19$, ε3/4 $n = 7$, ε4/4 $n = 1$) and 26 subjects with either probable AD (ε2/3 $n = 1$, ε3/3 $n = 5$, ε3/4 $n = 5$, ε4/4 $n = 2$) or amnestic mild cognitive impairment (ε2/3 $n = 1$, ε3/3 $n = 7$, ε3/4 $n = 5$). Medical history, physical exam, electrocardiogram and clinical laboratory screening were conducted to determine eligibility. All subjects were free from psychiatric disorders, alcoholism, severe head trauma, hypoxia, neurological disorders (except AD), renal or hepatic disease, diabetes (fasting glucose levels above 125 or any history of insulin or hypoglycemic agent use), chronic obstructive pulmonary disease, congestive heart failure or cardiac arrhythmias. With the exception of six AD subjects who were taking cholinesterase inhibitors, no subjects were taking medications with known CNS or glucose regulation effects. APOE and diagnostic groups did not differ with respect to age, gender distribution, education and body mass index (BMI). These subject characteristics are presented in Table 1.

2.2. Procedure

Subjects fasted for 12 h prior to receiving one of three conditions (saline, 20 IU insulin, 40 IU insulin) on separate mornings in randomized counterbalanced order. Subjects were placed in a supine position with the head tilted back. One-hundred microliters of insulin (Novolin R containing cresol, Novo Nordisk, Princeton, NJ, USA) or saline were administered with a needle-less syringe into alternating nostrils with a total administration volume of 400 μL. One-hundred microliters of insulin corresponded to 10 IU of insulin; a 20 IU dose of insulin was achieved with two administrations of 100 μL each of insulin and two administrations of 100 μL each of saline while a 40 IU dose of insulin was achieved with four administrations of 100 μL each of insulin. Subjects were instructed to sniff following administration to facilitate the transport of the insulin into the nasal cavity. Subjects rested for 15 min, after which a brief cognitive battery was administered. Blood was sampled at baseline and 45 min post-nasal administration for glucose and insulin analysis.

Table 1
Subject characteristics for normal control and memory-impaired groups by APOE-ε4 status

	Controls		Memory-impaired			
			MCI		AD	
	ε4− (n = 27)	ε4+ (n = 8)	ε4− (n = 8)	ε4+ (n = 5)	ε4− (n = 6)	ε4+ (n = 7)
Age (years)	75.4 ± 6.4	73.0 ± 5.2	76.8 ± 5.4	76.6 ± 3.7	76.7 ± 7.4	76.6 ± 5.3
Gender (female/male)	15/12	5/3	4/4	1/4	4/2	4/3
Education	15.3 ± 2.1	15.4 ± 2.3	14.0 ± 3.2	13.8 ± 3.6	13.3 ± 4.0	15.7 ± 2.1
Dementia rating scale	139.2 ± 4.1	141.0 ± 2.5	131.6 ± 6.9	129.0 ± 8.7	117.4 ± 14.6	124.5 ± 10.0
BMI (kg/m^2)	25.6 ± 3.0	25.9 ± 4.3	24.0 ± 3.8	24.3 ± 2.3	25.2 ± 1.7	25.4 ± 2.8
Cholinesterase inhibitor	0	0	2	0	2	2

Values are generally means ± S.D. Gender and cholinesterase inhibitor values are frequencies. There were no differences between APOE-ε4 or diagnostic groups for any characteristics other than dementia rating scale. BMI, body mass index.

Plasma glucose was measured with a glucose oxidase method using a glucose analyzer (Beckman Instruments, Fullerton, CA). Insulin was assayed as previously described [10]. The APOE genotypes were determined using the PCR conditions described by Emi et al. [19] and the Hhai restriction digest method of Hixson and Vernier [29].

2.3. Cognitive protocol

Three comparable versions of the cognitive protocol were constructed and randomly assigned in counterbalanced order to the three treatment conditions. The cognitive protocol assessed verbal declarative memory (story recall and a selective reminding word list task), visual working memory (Self-Ordered Pointing Task) [54], selective attention (Stroop Color-Word test) [26] and visual search [67]. On the story recall test [9], subjects heard a brief narrative containing 44 informational bits, and were asked to recall as much as possible both immediately and after a 10 min delay. Total verbatim recall was scored.

The selective reminding word list task was developed based on the Buschke Selective Reminding Test [8]. Subjects heard a list of 12 words drawn from three semantic categories and were asked to recall as many words as possible across five learning trials. After each trial, subjects were presented only the words that they failed to recall on the previous trial. Ten-minute delayed recall was also tested. The average number words recalled on the learning trials was added to the number of words recalled at the delay for a total recall score.

The Self-Ordered Pointing Task (SOPT) is a test of visual working memory. The test has two subtests with either 10 or 12 abstract designs appearing on a computer touch screen. On each subtest, subjects were asked to touch any one design that they had not touched previously. After each response, the designs in the array were rearranged. Trials continued until subjects had one opportunity to touch every design. Each subtest was repeated three times with the same designs. Numbers of errors on each trial were recorded.

The visual search task had two conditions. The first condition was a search task in which a single feature defined the target item; subjects were asked to touch a circle among squares on a computer touch screen. The second condition was a search task in which a conjunction of two features defined the target item; subjects were asked to touch a pink triangle among pink and green triangles, circles and squares. Reaction time for each trial was recorded.

The Stroop Color-Word task is a test of selective attention. In the first two conditions, subjects were asked to read color words, and to name colors as quickly as possible for 45 s. In the interference condition, subjects were required to name the ink color of color words printed in discordant colors (e.g. the word “red” printed in the color blue). Number of items completed within the time limit was recorded.

2.4. Statistical analysis

Inclusion of APOE genotype in the analyses was planned a priori based on prior research suggesting differential metabolic and cognitive responses to insulin administration in memory-impaired subjects of differing APOE genotypes [9,11,12,14]. For the normal group, initial analyses revealed no APOE-related differences in cognitive performance between normal ε4+ or ε4− adults, so they were collapsed into a single group. Subjects were thus divided into three groups: memory-impaired (MI)/ε4+ (n = 14), MI/ε4− (n = 12) and normal (n = 35). Percent change from baseline (20 or 40 IU insulin-saline/saline × 100) was calculated for cognitive scores and metabolic values for each of the three diagnostic groups. Percent change scores were subjected to mixed model repeated measures analyses of variance (ANOVAs). Diagnostic group (control, MI/ε4+, MI/ε4−) was entered as the between-subjects factors, and treatment condition (20 or 40 IU insulin) was the within subjects factor. T-tests were then applied to determine whether the percent change from baseline differed statistically from 0 (null hypothesis) for each group.

3. Results

3.1. Metabolic data

Intranasal insulin administration had no effect on plasma insulin or glucose levels for any of the diagnostic groups

Table 2
Plasma glucose and insulin values by treatment at baseline and 45 min after treatment

	Controls		Memory-impaired			
			ε4−		ε4+	
	Baseline	45 min	Baseline	45 min	Baseline	45 min
Glucose (mg/dL)						
Placebo	98 ± 11	101 ± 13	104 ± 13	100 ± 10	109 ± 18	113 ± 28
20 IU	101 ± 12	98 ± 11	105 ± 18	107 ± 21	109 ± 19	108 ± 23
40 IU	98 ± 11	97 ± 12	103 ± 14	102 ± 17	111 ± 22	104 ± 16
Insulin (μU/mL)						
Placebo	22 ± 10	21 ± 11	18 ± 8	17 ± 9	17 ± 7	14 ± 5
20 IU	21 ± 11	21 ± 10	18 ± 10	17 ± 7	18 ± 6	16 ± 7
40 IU	21 ± 11	21 ± 11	22 ± 10	21 ± 11	16 ± 6	16 ± 6

Values are means ± S.D. Intranasal insulin treatment resulted in no change in 45 min plasma insulin or glucose levels. NC, normal control.

(Table 2). Insulin and glucose levels did not differ when AD and MCI groups were compared directly.

3.2. Cognitive data

3.2.1. Verbal memory

For story recall, insulin produced significant memory improvement for the MI/ε4− group at both 20 and 40 IU doses (Fig. 1; $p = .0006$ and .0013). Neither the normal nor the MI/ε4+ group showed a significant change in story recall with insulin. At the 20 IU dose, improvement was greater for the MI/ε4− group than for the normal ($p = .0069$) or the MI/ε4+ group ($p = .0105$). A similar pattern was observed for the 40 IU dose (versus normal $p = .0051$; versus MI/ε4+ $p = .0252$). No differences were observed for insulin-induced changes in story recall, or in any measure, when AD and MCI groups were compared directly, or when DRS was used as a covariate.

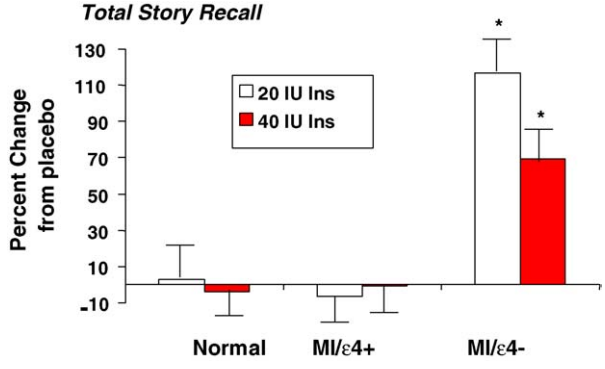

Fig. 1. Percent change in total story recall compared to placebo for controls and memory-impaired APOE ε4+ and ε4− groups. Story recall for MI/ε4− subjects was significantly improved with 20 ($p = .0006$) and 40 IU ($p = .0013$) of insulin compared with saline treatment. Mean raw score total recall at baseline was 39.9 (S.E. = 1.7) for normal control, 13.9 (S.E. = 2.7) for MI/ε4− subjects and 16.5 (S.E. = 2.0) for MI/ε4+ subjects. Following administration of 20 IU of insulin, total recall was 39.7 (S.E. = 1.8) for normal controls, 17.8 (S.E. = 2.7) for the MI/ε4− group and 12.8 (S.E. = 3.0) for the MI/ε4+. Following administration of 40 IU of insulin, total recall was 39.2 (S.E. = 1.9) for normal controls, 17.1 (S.E. = 3.0) for the MI/ε4− group and 15.0 (S.E. = 3.2) for the MI/ε4+.

The MI/ε4− group also had better performance following insulin administration for the Buschke Selective Reminding Test (Fig. 2). The effect was specific, however, for the 40 IU dose ($p = .0323$), for which the MI/ε4− group showed greater improvement than the MI/ε4+ group ($p = .0005$). Interestingly, the MI/ε4+ group showed reduced performance in the 40 IU condition relative to baseline ($p = .0044$). Buschke performance was unchanged at the 20 IU dose for all groups. The pattern did not differ when AD and MCI group membership was included as an independent variable, or when DRS was included as a covariate in the model.

3.2.2. Attention and working memory

In contrast to verbal memory, none of the attention or working memory tests showed an effect of intranasal insulin treatment on performance (data not shown). On the SOPT,

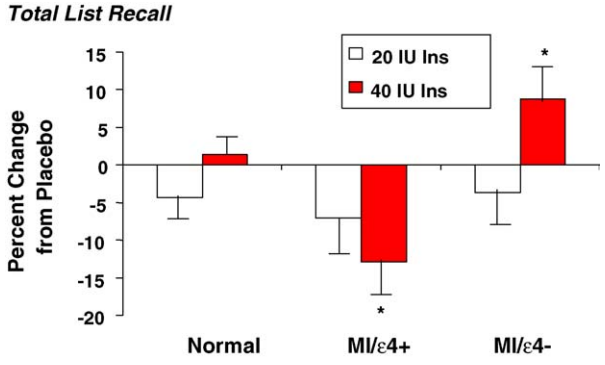

Fig. 2. Percent change in total word list recall compared to placebo for controls and memory-impaired APOE ε4+ and ε4− groups. Word list recall for MI/ε4− subjects was significantly improved with 40 IU of insulin compared with saline treatment ($p = .0323$). Word list recall for MI/ε4+ subjects was significantly lower with 40 IU of insulin compared with saline treatment ($p = .0044$). Mean raw score total list recall at baseline was 48.9 (S.E. = 1.8) for normal control, 31.2 (S.E. = 2.8) for MI/ε4− subjects and 31.3 (S.E. = 3.0) for MI/ε4+ subjects. Following administration of 20 IU of insulin, total list recall was 46.2 (S.E. = 1.9) for normal controls, 30.2 (S.E. = 2.9) for the MI/ε4− group and 31.1 (S.E. = 3.1) for the MI/ε4+. Following administration of 40 IU of insulin, total list recall was 49.5 (S.E. = 2.2) for normal controls, 33.3 (S.E. = 3.3) for the MI/ε4− group and 27.8 (S.E. = 3.6) for the MI/ε4+.

the MI and normal control groups did not show a change in errors with either 20 or 40 IU of insulin. In addition, the effects of treatment did not differ between MI and controls groups ($p = .96$).

Intranasal insulin treatment did not affect speed of target identification for either visual search test condition in any subject group. The effects of treatment did not differ between MI and control groups ($p = .41$).

Similarly, intranasal insulin treatment did not affect selective attention in the MI and normal control groups as measured by the Stroop Color-Word test. The effects of treatment did not differ between MI and control groups.

3.2.3. Adverse events

Two adverse events were reported during the study. One subject experienced a minor nosebleed that lasted for several minutes the evening after receiving 40 IU insulin. A second subject experienced nose soreness for about 24 h that began when the needleless syringe was inserted into the nasal cavity.

4. Discussion

Acute intranasal insulin administration improved verbal memory in AD and MCI subjects without the APOE-ε4 allele without changing plasma insulin or glucose levels. These results are consistent with previous literature that demonstrated verbal memory facilitation in memory-impaired ε4− subjects following peripheral elevations of insulin while maintaining euglycemia [9,11,12]. Prior studies have demonstrated that intranasal insulin administration results in acute elevations of CSF insulin [6] and changes in evoked brain potentials [34]. This is the first study in memory-impaired subjects to demonstrate that insulin's typical memory enhancing effects are observed following an intranasal administration technique. Our findings suggest that nasal administration results in acute cognitive effects without affecting peripheral insulin or glucose levels.

The findings of this study add further weight to the literature demonstrating that cognitive responses to acute insulin administration may vary according to APOE-genotype [9,11,12]. Twenty and 40 IU of insulin facilitated story recall for ε4− MI adults. Forty IU of insulin facilitated recall on a word list learning task for ε4− MI subjects. The facilitation of story recall at a lower dose than other cognitive tests may be due, in part, to the fact that story recall is one of the most sensitive measures of memory loss in early AD [63]. In addition, the story recall and list learning tests measure different aspects verbal memory; story recall is a test of contextual verbal memory which has additional demands on verbal organization and syntactic skills compared to the word list recall task [39,68]. No effects of treatment were observed on tests of attention. These selective cognitive effects are consistent with a recent intranasal insulin study that reported selective facilitation of verbal memory in healthy, young adults [4]. In our study, the ε4+ group showed no cognitive facilitation. In fact, for some measures, treatment may have reduced the cognitive performance of MI ε4+ subjects. This pattern may indicate that these doses were too high for ε4+ subjects. A previous dose response study suggested that ε4+ subjects may show cognitive facilitation at very low doses of insulin [9]. Alternatively, treatment response differences between APOE groups may reflect differences in the amount of insulin transported to the CNS following intranasal administration. This possibility could not be tested, as central insulin levels were not measured. These issues require additional study.

The effect of APOE genotype on cognitive and metabolic responses to insulin may reflect a specific pattern of abnormal insulin metabolism among ε4− subjects. For example, in a previous study, ε4− AD patients showed reduced insulin-mediated glucose disposal compared to ε4+ patients [12], results that are consistent with insulin resistance. ε4 non-homozygous patients had higher plasma insulin levels and lower CSF-to-plasma insulin ratios compared to ε4 homozygotes [14]. In addition, a recent study of insulin dose–response effects on memory in Alzheimer's disease found that non-ε4 homozygotes required higher insulin doses than ε4 homozygotes to induce memory facilitation [9]. This finding is consistent with increased insulin resistance in the non-ε4 homozygote group, as chronic hyperinsulinemia reduces brain insulin uptake [60,62], increasing the amount of insulin required for a similar memory effect. In the present study, the differential cognitive responses for APOE-ε4 groups, in conjunction with this literature, suggest that a lower intranasal insulin dose may be indicated for the ε4+ group.

Intranasally administered insulin may access the brain through several specific pathways [65]. The most likely route responsible for the acute effects observed in this study is an extraneuronal pathway in which bulk flow transports insulin through channels connected to brain parenchymal tissue or CSF [22]. Thorne et al. recently investigated intranasal pathways and mechanisms of transport to the CNS [66]. Autoradiographic comparisons of rats receiving intranasal or intravenous insulin-like growth factor-I (IGF-I) supported two extracellular pathways to the CNS. IGF-I appeared to rapidly travel through the channels connecting the nasal cavity with the olfactory bulbs and rostral brain regions to reach the parenchyma. They also provided strong support for a pathway through channels associated with the peripheral trigeminal system that connect the nasal cavity with the brain stem and spinal cord. There is additional support for a third extracellular pathway in which drugs quickly access the CSF after absorption into the submucosa along the olfactory nerve and cribriform plate [6,22,66]. Interestingly, the regions with the highest signal intensity included the hippocampus and amygdala. Given that insulin and IGF-I are similar in receptor structure [17,49], and both appear to bind to each other's receptors [49], these findings may have specific relevance for our results.

Not all drugs can access the CNS through intranasal pathways. A recent study failed to detect a direct nose-to-brain

pathway for melatonin and hydroxocobalamin [46]. However, the authors noted that these agents are more readily absorbed into the periphery than a peptide such as insulin. Thus, some agents may not be transported directly from the nasal cavity to the brain, or larger doses may be required for transport along this pathway. Insulin, however, demonstrates very poor transport across the nasal mucous membrane into blood [33]. In addition, our results demonstrate no changes in plasma insulin or glucose levels with treatment, strongly suggesting that the observed cognitive effects are not due to any significant transport from the nose to systemic circulation.

The specific mechanism of cognitive improvement requires additional study. Insulin affects multiple mechanisms related to neuronal activity. For instance, insulin affects specific regional glucose use in the brain. Although hyperinsulinemia does not affect whole-brain glucose use, hyperinsulinemia in rats changed glucose metabolism in the hypothalamus, amygdala, geniculate, suprachiasmic nucleus, supramammillary bodies and locus coeruleus [16]. In humans, low doses of insulin increased cerebral glucose metabolism in the cortex [5]. In addition, insulin may induce long-term potentiation through its influence on NMDA receptor activation [61]. Insulin also affects CNS concentrations of acetylcholine and norepinephrine, which are known to affect cognition [21,37]. Many effects of insulin, including its effects on cognition, are dose dependent [9]. Supplementing low brain insulin levels appears to facilitate cognition [10,13,35,50], but increasing insulin to high levels can impair cognition, especially when euglycemia is not maintained [36,37].

Raising low brain insulin levels may also have a direct effect on the pathophysiology of AD, although these effects are more likely to result from chronic changes in insulin levels. In a recent paper, Schubert et al. [59] abolished insulin signaling in vivo with a conditional knockout mouse model in which the insulin receptor gene was inactivated in the CNS. Phosphorylation of Akt and glycogen synthase kinase (GSK)3β was reduced and phosphorylation of tau increased 3.5-fold. These results suggest that reduced insulin signaling may increase hyperphosphorylation of tau, one of the neuropathological hallmarks of AD.

Low brain insulin may also influence CNS levels of Aβ, a second hallmark of AD. Reduced CNS insulin, receptor numbers and signaling events in AD may result in chronic and increasing deficits in brain oxidative metabolism and ATP. The resulting intracellular acidosis may increase Aβ production [31]. Low brain insulin may also reduce the release of Aβ from intracellular to extracellular compartments, given that insulin accelerates the trafficking of Aβ and its precursor from the Golgi and trans-Golgi network to the plasma membrane [24]. Insulin also regulates expression of insulin degrading enzyme, the protease that degrades Aβ [70]. Low levels of CNS insulin reported in subjects with AD without the APOE-ε4 allele may therefore increase the risk of elevated Aβ production and reduced degredation. Supporting these possibilities, Ho et al. [30] recently found that diet-induced insulin resistance in a transgenic mouse model of AD (Tg2576) caused 2-fold increases in $A\beta_{-40}$, $A\beta_{1-42}$, and amyloid plaque burden in select brain regions compared with non-insulin resistant mice. Insulin receptor abnormalities, reduced IDE levels, and cognitive impairment were observed in the insulin resistant mice relative to controls. It is possible that the effects of insulin abnormalities on the neuropathology of AD depend on the degree of the glucoregulatory disturbance. Similar to other dose–response effects of insulin described above, significantly high or low levels of insulin may have negative effects on Aβ levels. This literature suggests that normalizing low brain insulin levels through intranasal administration may reduce neuropathological changes related to AD.

Our results have potential implications for the treatment of AD. Although it is well established that acute insulin administration improves memory in AD patients, treatment with insulin has not been a viable option due to the risks associated with hypoglycemia. The cognitive benefits observed in a subgroup of memory-impaired subjects in this study raise the possibility that intranasally administered insulin may be a viable treatment option without the risk of systemic hypoglycemia. Additional support comes from other investigators who showed that intranasal insulin is safe in non-diabetic adults, even when higher doses (60 IU) were used with daily applications for 3 weeks [38].

In summary, our results demonstrate that intranasal insulin administration improves verbal memory in AD subjects without the APOE-ε4 allele. Additional research is needed to confirm these findings and to determine optimal dosing. In addition, future research is needed to determine if chronic intranasal insulin treatment holds promise for the treatment of cognitive symptoms for patients with memory impairment.

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