Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Intranasal Insulin

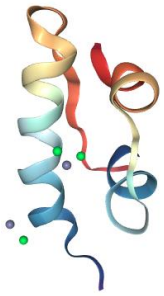
Evidence Summary

Some evidence suggests that intranasal insulin may be beneficial for Alzheimer's disease, though it will depend on the patient population and the delivery device.

Neuroprotective Benefit: Preliminary studies suggest intranasal insulin can improve cognition in healthy individuals and ApoE4- (regular insulin)/ApoE4+ (long-acting insulin) MCI/Alzheimer's patients. Though a large clinical trial in Alzheimer's patients failed, it may have been due to device malfunction.

Aging and related health concerns: There are some beneficial changes in biomarkers associated with intranasal insulin, though whether this would change clinical outcomes is not known.

Safety: Intranasal insulin is associated with few side effects not related to intranasal delivery itself.

Availability: OTC in some states; available with prescription; device must be bought from manufacturer	**Dose**: 20 IU bid (Alzheimer's); 40 IU 4x day (healthy)	**Chemical formula:** $C_{256}H_{381}N_{65}O_{76}S_6$ **MW**: 5777.603g/mol Source: Pubchem 
Half life: (In periphery): regular insulin (5-7 minutes), insulin detemir (5-7 hours)	**BBB**: Penetrant	
Clinical trials: 8 in Alzheimer's, 7 in healthy subjects	**Observational studies**: 0	

What is it?

Diabetes is a well-known risk factor for Alzheimer's disease and mild cognitive impairment (HR ~1.5 for both; Biessels and Despa, 2018). Although most studies do not suggest that diabetes increases the levels of typical Alzheimer's pathologies (amyloid plaques and tau tangles), it may cause cognitive impairment through other mechanisms such as damage to the cerebral vasculature, impaired insulin signaling in the brain, or glucose hypometabolism (Benedict and Grillo, 2015).

Insulin receptors are expressed in all cell types in the brain, though there are variations in expression between brain regions. Insulin enters the brain through active transport, though some controversial work suggests it can also be produced within the CNS. Insulin has many effects in the brain. In neurons it may modulate synaptic plasticity and the localization of ion channels and receptors. Glucose utilization in neurons can be influenced by, but is not required by, insulin signaling. In glia cells, insulin may modulate glucose uptake across the blood brain barrier and modulate inflammatory responses. Insulin signaling in the hypothalamus may also mediate peripheral metabolic responses (Arnold et al, 2018).

It is thought that chronic increased levels of insulin in the periphery due to an insulin-resistant state may cause insulin resistance in the CNS as well. Most studies suggest impaired insulin signaling in the brain of patients with Alzheimer's disease and T2DM, though the details of the signaling impairment are sometimes contradictory (more information below). Insulin signaling in the brain is complex. Insulin binds to insulin receptors (IRs) and then signals through the insulin receptor substrate (IRS)-PI3K-AKT pathway (Bedse et al, 2015).

It is generally thought that reduced pan tyrosine phosphorylation of the IRS-1 receptor (pY-IRS-1) and increased serine phosphorylation of the IRS-1 receptor (p-S^{312}-IRS-1, p-S^{616}-IRS-1) are indicative of insulin resistance.

Due to impaired cerebral insulin signaling in Alzheimer's disease and T2DM, many studies have explored the use of intranasal insulin as a potential therapeutic strategy. Little intranasal insulin enters the periphery; thus, the side effects of chronic peripheral insulin can be bypassed (e.g., hypoglycemia). Additionally, although insulin is actively transported across the blood brain barrier, transport may be affected by obesity, inflammation, glycemia, T2DM and circulating triglycerides (and possibly Alzheimer's disease) (Arnold et al, 2018). Born et al (2002) reported CSF levels of insulin increased after intranasal administration (40 IU) within 10 minutes and lasted the duration of the study (80 minutes) with no corresponding increase in serum insulin levels. Thus, intranasal insulin may have cognitive benefits without the side effects of chronic peripheral insulin treatment.

Types of insulin:

- Regular (Humulin R, Novolin R, Velosulin R)
- Rapid-acting (Insulin glulisine – Aprida; insulin lispro – Admelog, Humalog; insulin aspart – Fiasp, NovoLog)
- Long-acting (degludec – Tresiba; detemir – Levemir, glargine – Basaglar, Lantus)

Neuroprotective Benefit: Preliminary studies suggest intranasal insulin can improve cognition in healthy individuals and ApoE4- (regular insulin)/ApoE4+ (long-acting insulin) MCI/Alzheimer's patients. Though a large clinical trial in Alzheimer's patients failed, it may have been due to device malfunction.

Types of evidence:

- 8 studies in Alzheimer's patients
- 7 studies in healthy individuals
- Multiple biomarker studies of insulin resistance
- Multiple preclinical studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

The following chart summarizes the completed clinical trials using intranasal insulin in healthy individuals. A narrative review follows. Insulin refers to regular insulin unless otherwise stated (e.g. rapid-acting insulin).

Key: Significant Benefit; Significant Detriment; No change

Study	Drug	Population	Number	Length	Cognitive outcomes	Effect size (from Shemesh et al, 2010)	Other outcomes
Acute administration							
Benedict et al, 2007	Insulin, rapid-acting insulin (4 x 40 IU)	Healthy young adult men (18-35)	36	1 week	Immediate word recall, delayed word recall		
Benedict et al, 2008	Insulin (160 IU)	Healthy young men and women (avg age 22)	32	Acute	Immediate recall (women), IR (men), verbal working memory (women), VWM (men), hippocampal-independent task	IR (women): 0.26 VWM (women): 0.67 IR (men): -0.31 VWM (men): -0.44	Plasma glucose, insulin
Krug et al, 2010	Insulin (160 IU)	Post-menopausal women	14	Acute	Immediate recall, verbal working memory, hippocampal-	IR: 1.73 VWM: 1.24	

					independent task		
Long-term							
Benedict et al, 2004	Insulin (4 x 40 IU/day)	Healthy young adults (18-34)	38	8 weeks	Immediate word recall, delayed word recall, attention, mood	IR: 0.09 DWR: 0.74	Plasma glucose, insulin, cortisol
Benedict et al, 2007	Insulin, rapid-acting insulin (4 x 40 IU/day)	Healthy young adult men (18-35)	36	8 weeks	Immediate word recall, delayed word recall (DWR)	IR (insulin): 0.02 IR (RA-insulin): 0.04 DWR (insulin): 0.85 DWR (RA-insulin): 2	Plasma glucose, insulin
Hallschmid et al, 2008	Insulin (4 x 40 IU/day)	Obese men	30	8 weeks	Immediate word recall, delayed word recall	DWR: 0.94	Plasma cortisol, ACTH, weight
Ritze et al, 2018	Insulin (160 IU evening vs. morning)	Healthy young adult men (avg age 27)	36	8 weeks	Immediate word recall (morning), IR (evening), delayed word recall (morning), DWR (evening)		

Acute Studies

Acute treatment with insulin (160 IU) improved immediate recall and verbal working memory in healthy young women but not men. There were no improvements in a hippocampal-independent task. There were reductions in blood glucose but no increase in insulin (Benedict et al, 2008). In post-menopausal women, insulin (160 IU) improved verbal working memory but not immediate recall or performance on a hippocampal-independent task (Krug et al, 2010). In healthy young adult men, rapid-acting and regular insulin over one week had no effect on memory (Benedict et al, 2007).

The authors of the previous studies speculate that different effects of intranasal insulin on sex may be due to the fact that it has anorexigenic effects in men (men sometimes eat less with intranasal insulin) because of its effect on the hypothalamus, and it has memory enhancing effects on women. This could be due to the differential effects of sex hormones and their interactions with insulin signaling.

Sub-chronic Studies

In an RCT of 38 healthy young adults (age 18-34), intranasal insulin (4 x 40 IU/day) had no acute effects. An 8-week treatment improved delayed (but not immediate) word recall and had no effect on attention. Certain aspects of mood (e.g. self-confidence and well-being) also improved. There were no effects on plasma glucose or insulin levels, though plasma cortisol levels were reduced. This could be due to intranasal insulin's effect on the hypothalamus (Benedict et al, 2004). Using data from the regular insulin-treated group from the previous study, Benedict et al (2007) looked at the effects of rapid-acting insulin aspart (Insulin NovoLog, 4 x 40 IU/day) over 8 weeks in 36 healthy young adult men (age 18-35). Both groups (regular and rapid-acting) had improved scores on delayed (but not immediate) word recall after 8 weeks with the rapid-acting insulin group performing even better than the regular insulin group. Similar cognitive results were also found in obese men after 8 weeks of regular insulin (4 x 40 IU/day) treatment, with additional reductions in serum cortisol and adrenocorticotropic hormone (ACTH). No changes were found for attention (Hallschmid et al, 2008).

Comparing the effects of morning versus evening intranasal insulin (160 IU in a single dose) over 8 weeks in 36 healthy men, Ritze et al (2018) found that evening insulin improved delayed (but not immediate) recall compared to placebo at 5 weeks (but not 8 weeks).

***Human research to suggest benefits to patients with dementia*:**

Evidence for insulin resistance in the brains of patients with Alzheimer's disease

Multiple post-mortem studies suggest impaired insulin signaling in the brains of patients with Alzheimer's disease. In 54 patients, Steen et al (2005) reported reduced levels of insulin growth factor (IGF)1-R, IGF2-R, IR, IGF-1, IGF-2, IRS-1, IRS-2, and insulin mRNA in multiple brain regions. In contrast, Moloney et al (2010) reported an increase in IGF1-R *protein* expression in Alzheimer's patients, though IGF1-R protein was highly expressed in astrocytes and colocalized with amyloid plaques and tau tangles. Although Moloney et al (2010) found similar expression of the IR protein in Alzheimer's and control brains, in control neurons IR was expressed throughout the cell soma while in Alzheimer's neurons it was largely localized around the nucleus. They also reported a decrease in IRS-1/2 and an increase in p-S^{312}-IRS-1 and p-S^{616}-IRS-1 expression. Talbot et al (2012) found an increase in IRS-1, p-S^{312}-IRS-1, p-S^{616}-IRS-1 and a decrease in IR/IGF-1Rβ-pY in hippocampal CA1 neurons.

Impaired insulin signaling was also reported in post-mortem tissue from patients with Alzheimer's, T2DM, and Alzheimer's w/T2DM, with the greatest effect in patients with both Alzheimer's and T2DM. There was an inverse correlation between expression of many proteins involved with insulin signaling and tau phosphorylation, suggesting reduced insulin signaling in areas with increased p-tau (Liu et al, 2011). In addition, *ex vivo* studies suggested that hippocampal and cerebellar tissue from Alzheimer's patients show reduced responsiveness to insulin and IGF-1 and an inverse correlation between episodic memory and p-S^{616}-IRS-1 expression in hippocampal neurons (Talbot et al, 2012).

In a cross-sectional study of 62 patients with either aMCI/AD, T2DM, FTD, or controls, Kapogiannis et al (2015) reported increased insulin resistance (defined as the insulin resistance index (R) – the ratio of p-S^{312}-IRS-1/p-Y-IRS-1) in neuronally-derived extracellular vesicles (EVs) in patients with Alzheimer's disease and T2DM. Furthermore, in a retrospective analysis of blood samples collected up to 10 years before the diagnosis of Alzheimer's, insulin resistance increased in EVs, suggesting that insulin resistance in the brain occurs before the onset of clinical symptoms. Mullins et al (2017) reported that in 24 patients with biomarker supported aMCI/Alzheimer's disease, brain volume in the right middle/superior temporal gyri positively correlated with p-Y-IRS-1 and inversely correlated with p-S^{312}-IRS-1 in neuronally-derived blood exosomes, suggesting that improved insulin sensitivity was correlated with increased brain volume. The regions of correlation with p-Y-IRS-1 corresponded to regions where IRS-1 is expressed from brain tissue from healthy subjects in the Allen Brain Atlas.

Evidence for the use of intranasal insulin

The following chart summarizes the completed clinical trials using intranasal insulin. A narrative review is below.

Key: Significant Benefit; Significant Detriment; No change

Terms:

Dementia Severity Rating Scale (DSRS) – a measure of function in patients with dementia

Study	Phase	Drug	Population	Number of patients	Length	Cognitive outcomes	Alzheimer's biomarkers outcomes	Other outcomes
Insulin detemir (long-acting)								
Claxton et al, 2015	2	Insulin detemir (10 IU b.i.d or 20 IU b.i.d.)	aMCI/mild-moderate AD	60	21 days	E4+ verbal memory; E4- verbal memory; verbal/visuospatial memory		E4+ HOMA-IR; E4- HOMA-IR
Craft et al, 2017	2	Insulin detemir (20 IU bid)	aMCI/mild-moderate AD	36	4 months	ADAS-cog; DSRS; Memory composite	2/12 MRI Brain region volume; CSF AB42, tau, ptau, ptau/AB42	
Regular insulin								
Craft et al, 2012	2	Insulin (10 IU bid)	aMCI/mild-moderate AD	104	4 months	Memory; ADAS-cog; DSRS; ADCS-ADL (only ApoE4- patients)	CSF AB40, AB42, tau; FDG-PET	
		Insulin (20 IU bid)		104		Memory; ADAS-cog; DSRS; ADCS-ADL (only ApoE4- patients)	CSF AB40, AB42, tau; FDG-PET	

Craft et al, 2017		Insulin (20 IU bid)	aMCI/mild-moderate AD	36	4 months	ADAS-cog; DSRS; Memory composite	4/12 MRI brain regions; CSF AB42, tau, ptau, ptau/AB42; change insulin signaling from EV	
Reger et al, 2008		Insulin (20 IU bid)	aMCI/Alzheimer	25	21 days	Memory; Attention; DSRS – all compared to baseline		
Acute insulin treatment								
Reger et al, 2006		Insulin (20, 40 IU)	aMCI/Alzheimer	92	Acute	Story/word recall (ApoE4- patients); word recall (ApoE4+ patients), story recall (ApoE4+ patients)		
Reger et al, 2008		Insulin (10, 20, 40, 60 IU)	aMCI/Alzheimer	26	Acute	Story/word recall (in ApoE4-, not ApoE4+ at 20 IU)		
Rosenbloom et al, 2014	2	Rapid-acting insulin glulisine (20 IU)	Mild-moderate Alzheimer	12	Acute	Memory, attention, language, visuospatial function		

Acute treatment

Acute treatment of individuals with aMCI/Alzheimer's with intranasal insulin improved delayed (but not immediate) story recall and delayed and immediate word recall in ApoE4- (but not ApoE4+) patients at 20 IU (other doses – 10, 40, and 60 IU – were largely ineffective) (Reger et al, 2008). These results were similar to a previous study where 20 IU and 40 IU improved story and list recall (40 IU only for list recall) in ApoE4- patients. Interestingly, 40 IU was detrimental to list recall in ApoE4+ patients (Reger et al, 2006). Another study tested the acute effects of rapid-acting insulin glulisine (20 IU) in ApoE4+ mild-moderate Alzheimer's patients and found no effect after treatment (Rosenbloom et al, 2014).

Sub-chronic treatment

Craft et al (2012) treated 104 patients with aMCI/mild-moderate Alzheimer's disease with insulin (10 or 20 IU bid) over 4 months. Patients treated with 20 IU insulin, but not 40 IU insulin, had improved memory scores. In both groups there were improvements on the DSRS and ADAS-cog. There was less functional decline (measured with ADCS-ADL) in patients with Alzheimer's disease but not MCI. Although there were no significant changes in CSF markers (Aβ42, Aβ40, tau) in treated patients, CSF Aβ42 and tau/Aβ42 levels correlated with improved memory and function. Also, there was a reduction in the progression of hypometabolism (measured with FDG-PET) in five brain regions compared to placebo. Although there were no changes in markers for insulin resistance in neuronally-derived extracellular vesicles, in the 20 IU group, changes in insulin signaling from isolated serum extracellular vesicles correllated with cogntion as a group and in ApoE4- (but not ApoE4+) patients (Mustapic et al, 2019).

Based on this data, a phase 2/3 study was initiated using 20 IU bid in 289 patients with aMCI/mild Alzheimer's over one year. The delivery device that had been used in previous trials (Kurve Technology's ViaNase) was redesigned and frequently malfunctioned. Therefore, the investigators switched to NeuroPharma's Precision Olfactory Delivery device. There were no improvements in cognition or Alzheimer's CSF biomarkers, and treated patients had increased hippocampal shrinkage. In a subgroup analysis of those who had completed the trial using the ViaNase device (n=49), there was improved cognition at 6 months (though not at 12 months).

In contrast, in an RCT of 60 patients with aMCI/mild-moderate Alzheimer's disease, 20IU of intranasal insulin detemir (a long-acting insulin) over 21 days improved verbal and visual working memory. For verbal memory, *ApoE4+ patients improved while ApoE4- were worse* compared to placebo. These results reflected insulin resistance after the study with ApoE4+ patients becoming more insulin sensitive and

ApoE4- patients becoming more insulin resistant (measured with HOMA-IR). No differences were seen with a lower dose (10 IU bid) (Claxton et al, 2015).

This study contrasts the study of regular insulin in two ways: a higher dose was more beneficial, and ApoE4+ patients benefitted while ApoE4- patients were worse off. With regards to dosing, the authors speculate that insulin detemir has greater cumulative exposure and has less affinity for the insulin receptor which may affect the dosing. With regards to ApoE4, insulin detemir has greater lipophilicity and albumin-binding, and ApoE4+ individuals with Alzheimer's disease have greater vulnerability to albumin nitration which may affect the binding of insulin detemir to albumin in the brain.

A clinical trial comparing regular insulin (20 IU bid), insulin detemir (20 IU bid), and placebo in 36 patients with aMCI/probable Alzheimer's disease over 4 months reported mixed results. Although there were no changes in global cognition (ADAS-cog) or daily functioning, individuals treated with regular insulin had improved memory scores compared to placebo. There were no changes in memory in patients treated with insulin detemir, though at 2 months, but not 4 months, ApoE4+ patients treated with insulin detemir had improved memory scores compared to ApoE4+ placebo patients. Regular insulin-treated patients had increased brain volume (by MRI) in 4 out of 12 brain regions compared to placebo while insulin detemir-treated patients had reduced volume in 2 out of 12 brain regions. CSF biomarkers (AB42, tau, ptau) did not change, though the ptau/AB42 ratio improved in patients treated with regular insulin (Craft et al, 2017). There were likely too few patients in this study to draw a conclusion. In a smaller study (n=25) using regular insulin (20 IU bid) in patients with aMCI/Alzheimer's disease, treated patients had improved memory, attention, and DSRS compared to baseline with no change in the placebo group (Reger et al, 2008).

Conclusion

There are mixed results in clinical trials of intranasal insulin for Alzheimer's disease. Regular insulin at lower doses seem to benefit ApoE4- individuals, while insulin detemir (a longer-acting insulin) seems to benefit ApoE4+ patients at higher doses.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

In animal studies, intranasal insulin has improved markers of insulin signaling, reduced levels of amyloid (but not tau), increased levels of synaptic proteins, and reduced inflammation (Bedse et al, 2015; Chen et al, 2014)

APOE4

There are mixed results in clinical trials of intranasal insulin for Alzheimer's disease. Regular insulin at lower doses seem to benefit ApoE4- individuals, while insulin detemir (a longer-acting insulin) seems to benefit ApoE4+ patients at higher doses.

Aging and related health concerns: There are some beneficial changes in biomarkers associated with intranasal insulin, though whether this would change clinical outcomes is not known.

Types of evidence:

- 5 clinical studies on peripheral biomarkers

Most studies have examined the effect of intranasal insulin on the CNS. However, intranasal insulin may also act on the hypothalamus, causing peripheral effects.

Multiple studies reported that sub-chronic (8-week) intranasal insulin reduced blood levels of cortisol (Hallschmid et al (2008); Benedict et al (2004) – 40 IU, bid). Acute intranasal insulin (160 IU) was reported to reduce circulating levels of free fatty acids (but not triglycerides) and improve peripheral insulin sensitivity in lean, but not obese, men (Iwen et al, 2014; Heni et al, 2014). A 4-week treatment with intranasal insulin (40 IU, 4 x day) had no effect on hepatic lipid content but reduced circulating levels of branched chain amino acids (Scherer et al, 2017).

Safety: Intranasal insulin is associated with few side effects not related to intranasal delivery itself.

Types of evidence:

- One systematic review

One advantage of intranasal insulin is that it largely does not enter the periphery, thus does not affect periphery insulin or glucose levels. One study reported that high levels of intranasal insulin (160 IU) does slightly increase peripheral insulin levels, but not enough to affect glucose levels.

A recent review looked at all the intranasal insulin clinical trials among all indications (18 studies, 832 people, duration generally between 2-12 months). Although some studies reported slight reductions in serum glucose levels, no cases of symptomatic hypoglycemia were reported. No adverse events were

reported to be greater in the insulin group. The most common adverse events were due to the route of administration and included slight burning in the nasal cavity after administration and some cases of nasal cavity infections (Schmid et al, 2018). However, there are no large, long-term clinical studies.

Drug interactions:
Although little intranasal insulin enters the periphery, hypothetically it may interact with other glucose-lowering drugs. Major drug interactions for insulin include many antibiotics, though it is unclear if the same interactions occur with intranasal insulin (drugs.com).

Sources and dosing:
Intranasal insulin can be bought over the counter in some states or with a prescription. 160 IU (4 x 40 IU per day) used for healthy individuals, 20 IU (10 IU bid) of regular insulin for ApoE4- individuals with Alzheimer's disease, and 40 IU (20 IU bid) of insulin detemir for ApoE4+ individuals with Alzheimer's disease.

Most studies have used the ViaNase device for Alzheimer's disease. However, a recent clinical trial failed, and the investigators reported that it was redesigned and frequently malfunctioned. They switched to the NeuroPharma Precision Olfactory Delivery device. However, in a subgroup analysis, they found that individuals who had used the ViaNase device had improved cognition.

Research underway:
One study is ongoing for stroke (NCT02810392). Two studies are ongoing for post-operative cognitive decline/delirium (NCT03415061; NCT03324867). Two studies are ongoing in aMCI/Alzheimer's patients using fast-acting insulin (NCT02503501; NCT02462161). One study in patients with MCI is ongoing comparing the effects of two different devices (ViaNase, Impel POD; NCT03857321).

Search terms:
Intranasal insulin + alzheimer, memory, cognition, longevity, aging

Websites:
Clinicaltrials.gov
Pubmed

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