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Intranasal Insulin Therapy for Cognitive Impairment and Neurodegeneration: Current State of the Art

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Abstract

Introduction—Growing evidence supports the concept that insulin resistance plays an important role in the pathogenesis of cognitive impairment and neurodegeneration, including in Alzheimer's disease (AD). The metabolic hypothesis has led to the development and utilization of insulin- and insulin agonist-based treatments. Therapeutic challenges faced include the ability to provide effective treatments that do not require repeated injections and also minimize potentially hazardous off-target effects.

Areas covered—This review covers the role of intra-nasal insulin therapy for cognitive impairment and neurodegeneration, particularly Alzheimer's disease. The literature reviewed focuses on data published within the past 5 years as this field is evolving rapidly. The author provides evidence that brain insulin resistance is an important and early abnormality in Alzheimer's disease, and that increasing brain supply and utilization of insulin improves cognition and memory. Emphasis was placed on discussing outcomes of clinical trials and interpreting discordant results to clarify the benefits and limitations of intranasal insulin therapy.

Expert Opinion—Intranasal insulin therapy can efficiently and directly target the brain to support energy metabolism, myelin maintenance, cell survival, and neuronal plasticity, which begin to fail in the early stages of neurodegeneration. Efforts must continue toward increasing the safety, efficacy, and specificity of intranasal insulin therapy.

Keywords

Alzheimer's disease; diabetes mellitus; insulin-like growth factor; insulin resistance; insulin sensitizers; intranasal insulin; mild cognitive impairment; obesity; PPAR agonists

1. Introduction

a) Presence and Trafficking of Insulin in the Brain

Insulin polypeptide and insulin receptor are expressed in the mature and developing brains^{1–7}. Insulin receptor expression is widely distributed throughout the brain¹, but most abundant in cortical-limbic structures, including the olfactory bulb, hypothalamus, hippocampus, amygdala, and cerebral cortex (orbitofrontal and cingulate regions)^{3, 8, 9}, as

well as in the cerebellum^{10, 11}. Although debate continues concerning insulin synthesis in the brain, independent investigators have shown that the messenger RNA is expressed in neurons within the same regions that have high level receptor expression^{2, 3}. At the same time there is excellent evidence that insulin is taken up into the brain from the peripheral circulation¹, and following intranasal administration^{12, 13}. Although it is widely accepted that the most abundant source of insulin that traverses the blood-brain barrier originates from the pancreas, recent evidence indicates that insulin may be¹⁴ and insulin-like growth factors (IGFs)^{15, 16} are synthesized in nasal epithelium or serous glands. Insulin produced in the nasal cavities enters the central nervous system (CNS) directly through the cribriform plate, and is transported along the olfactory nerves into the brain parenchyma, and principally ventromedial limbic structures¹⁴. Alternatively, extra-CNS insulin traverses the blood-brain barrier via specific receptors to activate insulin-dependent functions and networks¹⁴.

b) Insulin and Insulin Receptor Functions in the Brain

Within the past 8 to 10 years, the roles of insulin in the brain have undergone intense scrutiny both in humans and experimental models. Insulin is a pleiotrophic hormone that has diverse functions in nearly every cell, including those of CNS origin. In the brain, insulin has critical roles in regulating neuronal functions such as growth, metabolism, plasticity, survival, and cholinergic function, which are needed for learning and memory^{9, 17–19}. Moreover, increased levels of CNS insulin enhance learning and memory by improving hippocampal function^{20–22}. Like insulin, leptin is another important regulator of food intake and metabolic processes such as lipid homeostasis, glucose utilization, and energy expenditure in the brain²³. Due to insulin's important roles in mediating neurocognitive function and energy balance, investigators focusing on the contributions of either peripheral insulin resistance or CNS insulin resistance have independently helped to shape the current body of literature and our present understanding of brain insulin resistance and its consequences.

c) Brain Insulin Resistance and Alzheimer's Disease

It is now well established that defects in insulin receptor signals correlate with dementia, particularly in AD^{2, 3, 24–26}. In addition, although cerebrospinal fluid (CSF) insulin levels can be normal or even elevated at different points in disease^{27, 28}, evidence suggests that CSF insulin declines with AD progression^{26, 29}. Postmortem studies demonstrated that in AD, brain insulin resistance is associated with reduced receptor expression, binding, tyrosine phosphorylation, and activation of the intrinsic receptor tyrosine kinase^{2, 3}. Correspondingly, downstream signaling networks that promote neuronal survival, plasticity, growth, and cholinergic function are inhibited^{2, 3, 7, 30–33}. Correspondingly, molecular, neuropathological, biochemical, and neurobehavioral abnormalities of the types seen in AD were produced in experimental animals by intracerebral administration of the pro-diabetes toxin, Streptozotocin^{17, 34, 35}, genetic depletion of brain insulin receptors or downstream effectors^{36, 37}, or molecular silencing of brain insulin and IGF receptors³⁸. The results of these studies indicate that brain insulin resistance is sufficient to cause brain metabolic dysfunction, cognitive impairment, and neurodegeneration. Furthermore, while it is still possible that brain insulin resistance represents an adaptive or protective response to

hyperinsulinemia, it is unlikely that this concept has major relevance to the CNS abnormalities in MCI or AD because : 1) most individuals with AD and brain insulin resistance do not have hyperinsulinemia ^{2, 3}; 2) experimental models of brain insulin resistance lead to neurodegeneration ^{17, 38, 39}; and 3) administration of insulin improves cognitive function in the early stages of AD when brain insulin resistance already exists ^{13, 40, 41}.

d) Experimental Models of Brain Insulin Resistance

Experimental data showed that siRNA silencing of the brain insulin receptor gene produces similar molecular and biochemical effects as occur in AD-type neurodegeneration ³⁸, and that the administration of a pro-diabetes toxin leads to loss of brain insulin receptor functions and attendant deficits in spatial learning and memory ¹⁷. The pivotal role of impaired insulin receptor function in relation to neurodegeneration was confirmed by reversal of the AD phenotype following treatment with insulin sensitizer drugs ⁴². Another important point is that aging-associated declines in CNS insulin levels most likely contribute to cognitive impairment and neurodegeneration ⁴³, as aging is the strongest risk factor for developing AD. Besides the direct consequences of brain metabolic dysfunction, insulin resistance reinforces the neurodegeneration cascade in exacerbating amyloid accumulation, neuronal loss, and synaptic disconnection ⁷. Altogether, the aggregate data support the hypothesis that Alzheimer's is a metabolic disorder in which brain insulin deficiency and resistance are at the core, and therefore shares molecular, biochemical, and pathophysiological features with diseases such as Type I and Type II diabetes mellitus ^{4, 6, 33, 44, 45}. Consequently a role for insulin therapy is justified in correcting the metabolic dysfunction.

e) Brain Insulin Resistance in Obesity

The second group of investigators focused heavily on the importance of insulin signaling in the brain are those interested in regulation of energy balance, satiety, and feedback loops between the brain and gut. There is now convincing evidence that obesity is linked to brain insulin resistance, cognitive impairment, and neurodegeneration ^{5, 18}. In normal physiological states, intranasal insulin exerts anorexic effects that negatively regulate food intake ⁴⁶. However, insulin resistance adversely affects the ability to achieve satiety and the regulation of caloric consumption ⁴⁷. Another factor possibly contributing to obesity pertains to the finding that insulin treatment lowers plasma and saliva cortisol levels in response to social stress ⁴⁸. In states of insulin resistance, insulin is less effective in attenuating stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis ⁴⁷, which could lead to stress-related disruption of energy balance due to excessive calorie consumption ^{49, 50}.

f) Potential contributions of Type 2 Diabetes and Hyperglycemia

Since the recognition that AD is associated with brain insulin resistance, a considerable body of literature has addressed the potential role of diabetes mellitus as a causal or co-factor in neurodegeneration. In a recent prospective longitudinal study, no significant relationship between peripheral glucose intolerance and insulin resistance could be demonstrated with respect to AD pathology ⁵¹. However, since the at risk subjects were

treated for diabetes, the full impact of diabetes on neurodegeneration was not adequately assessed. To this end, another recent study demonstrated significantly increased risk of dementia among diabetics and hyperglycemia in general ⁵². Therefore, in the pre-diagnostic phase of peripheral insulin resistance and diabetes, the CNS may be vulnerable to the consequences of hyperglycemia and/or hyperinsulinemia, or sustain progressive injury and degeneration due to simultaneous development of brain insulin resistance. These concepts are supported by the findings of impaired brain glucose utilization and deficits in memory functions in individuals with sub-clinical diabetes mellitus ⁵³. Furthermore, the finding that patients with AD+diabetes exhibited slower cognitive declines than those with AD alone ⁵⁴ could be interpreted as evidence that systemic treatment for diabetes/peripheral insulin resistance is neuroprotective.

2. Intranasal Insulin Therapy

a) Therapeutic Approach Rationale

Insulin can be administered through subcutaneous, transdermal, oral, sub-lingual, buccal, rectal, vaginal, intramuscular, intraperitoneal, and intranasal routes ⁵⁵. Intranasal delivery of insulin, as well as other compounds, is enabled by the direct neuroanatomical connections between the olfactory nerves and brain. This portal of access to the brain is advantageous because structural modifications of existing therapeutic compounds may not be required, particularly when they are small molecules. Another point is that drugs which could be used to treat neurological and psychiatric diseases may have limited therapeutic responses due to poor penetrance across the blood-brain barrier and therefore restricted ability to access the CNS. Intranasal therapy circumvents these problems while simultaneously reducing unwanted systemic responses. The discovery that nasal mucosa expresses and can deliver insulin to the brain suggests that nasal-to-brain transfer of insulin is physiological. Altogether, intranasal therapy provides a practical and noninvasive approach for treating cerebrovascular, behavioral, neoplastic, neurophysiologic, and diseases, and may also enable rapid and safe delivery of neuroprotective agents. Since normal neuroanatomical connections between the olfactory and limbic systems mediate memory, cognitive function, and behavior ⁵⁶, intranasal therapy could be used to target neurodegenerative and psychiatric diseases.

b) Insulin Supports Memory and Cognitive Function

Alzheimer's disease (AD) brains exhibit progressive insulin resistance and declines in insulin levels with severity of neurodegeneration ^{2, 20}. Neuro-imaging studies linked in vivo brain insulin resistance to neurodegeneration by demonstrating significant perturbations in insulin regulated metabolism, and correlations between increased brain insulin resistance and reduced cerebral volume, impaired responses to insulin, and hippocampal atrophy in AD, Type 2 diabetes, and obesity ¹³. Increasing brain insulin levels improves verbal and hippocampal declarative memory ^{12, 57}, and in AD, insulin improves cognitive function and slows cognitive decline ^{8, 44}. Together, these observations support the concept of insulin-based therapy for AD ⁵⁸, including prevention and treatment ¹³.

Intranasal insulin therapy provides an excellent means of supplying the brain with insulin to overcome deficits in production, transport, and responsiveness, reproducing the effects of systemic insulin but with avoidance of adverse effects. Intranasal insulin improves cognitive function with respect to attention, and verbal and hippocampal declarative memory^{12, 57, 59}. Clinical trials data have shown that in subjects with MCI or AD, intranasal insulin improves memory and metabolic function¹³. However, sub-group analysis revealed that following intranasal insulin administration, subjects who had an apolipoprotein E- ϵ 4 (APOE- ϵ 4) negative genotype exhibited significant improvements in verbal memory, whereas those who were APOE- ϵ 4 positive had poor responses on recall tasks^{60, 61}. The therapeutic efficacy of intranasal insulin has now been confirmed by a number of independent studies²⁶. The consistent findings were that, among individuals who had brain insulin resistance associated with MCI, early AD, or Type 2 diabetes mellitus, significant improvements in cognition, memory, attention and metabolic function occurred within a few months of treatment in the clinical trials^{26, 41, 62, 63}. Mechanistically, in addition to the stimulatory effects on energy metabolism, insulin increases amyloid clearance from the brain⁶⁴ and it supports neuronal cytoskeletal and cholinergic functions^{6, 9, 11}. Furthermore, enhanced insulin signaling inhibits the activity of kinases that promote tau hyperphosphorylation, and activates pathways that mediate synapse formation and neuronal plasticity⁶⁵. Although increasing availability of insulin is expected to restore insulin's actions in the brain, the insulin resistant neurons and glial cells may not be responsive. Instead, the connecting neurons that are insulin responsive but dependent upon activity-dependent connections from insulin resistant cells might be preserved. In addition, as in type 2 diabetes, providing higher levels of insulin to insulin resistant cells could also be an important means of maintaining function.

c) Intranasal Insulin and Reversal of Obesity

Overall, CNS energy balance is mediated by hypothalamic neuropeptide pathways that enable peripheral adipose tissue to signal body fat content information to the brain via insulin and leptin^{47, 66, 67}. These processes are distinct from those involved in hippocampal function, verbal memory, and attention^{8, 68}. Besides increasing cognitive performance, chronic intranasal insulin administration reduces adiposity in normal individuals⁶⁹. Functional magnetic resonance imaging studies showed that in healthy individuals, intranasal insulin reduces brain activity in response to food picture stimuli⁷⁰, whereas in obese subjects, insulin-stimulated visual evoked (food modulated) responses are reduced⁷¹. In another study of obese individuals, insulin was observed to improve memory without significantly affecting body fat⁷². In addition, intranasal insulin was demonstrated to alter activity in the hypothalamus, which regulates homeostatic and reward-related functions⁷³. These findings suggest that brain insulin resistance can differentially affect cognitive and metabolic signaling pathways.

Further studies demonstrated gender-specific differences in response to intranasal insulin. Men were found to be more sensitive than women to appetite/anorexigenic and metabolic effects of intranasal insulin^{69, 74}, while both pre- and postmenopausal women were found to be more sensitive to insulin stimulation of hippocampus-dependent memory functions^{74, 75}. In a recent all-women study, insulin responsiveness to body mass index was demonstrated to be localized in the prefrontal and anterior cingulate cortex⁷⁶. These observations suggest

that insulin regulates food intake by modifying reward activity in the brain, and that insulin resistance contributes to obesity by short-circuiting this pathway. This suggests that, under normal circumstances, insulin promotes satiety and thereby helps regulate food intake.

d) Intranasal Insulin for Treatment in Individuals with Diabetes Mellitus

The main emphasis of this review is to consider the advantages and complications of intranasal insulin therapy for treating mild cognitive impairment and AD. However, it is important to recognize that the same approach is utilized to treat systemic insulin resistance and deficiency, raising questions about specificity and potential off-target effects of therapy designed to treat neurodegeneration. One limitation of using intranasal insulin to treat diabetes mellitus is that sufficient peripheral blood levels must be achieved to restore glucose homeostasis. On the other hand, in the setting of diabetes mellitus, intranasal insulin could be used to prevent secondary effects of disease, including cognitive impairment. For example, in a murine model of type I diabetes produced by Streptozotocin administration, progressive cognitive impairment and white matter atrophy were correlated with brain insulin resistance. Treatment with intranasal insulin prevented the brain morphological abnormalities, white matter loss, and impairments in signaling through survival and synaptic plasticity pathways ⁷⁷. In another animal model that more closely mimics human disease, mucosal administration of autoantigens prevented type 1 diabetes ⁷⁸. However, attempts to use intranasal insulin to prevent type I diabetes shortly after detection of autoantibodies proved unsuccessful ⁷⁹.

e) Intranasal Insulin-Like Growth Factor, Type 1 (IGF-1) Treatment

Insulin and IGF-1 activate very similar signaling pathways, utilizing their own receptors, and achieving distinct but related outcomes. Like insulin, IGF-1 and IGF-1 receptors are abundantly expressed in the brain ⁹. IGF-1 signaling mediates neuronal growth, migration, regeneration, and repair ⁹. In an experimental model of spinal cerebellar atrophy, intranasal IGF-I therapy helped improve motor performance and partial recovery of Purkinje cell protein expression and function ⁸⁰. In another study, investigators used intranasal IGF-I to treat middle cerebral artery occlusion models of stroke. The findings were significant reductions in infarct volumes even when administered between two or four hours after vascular occlusion. On a histologic level, the reduction in infarct volume is associated with decreased apoptosis and tissue injury and functionally there was significantly greater recovery of motor and sensory systems compared with vehicle ⁸¹. Subsequent studies demonstrated effectiveness of IGF-I for reducing infarct volume or hypoxic – ischemic injury in the brain ^{82, 83}. In addition the neuroprotective actions of IGF-I and its ability to support neurogenesis suggests a potential therapeutic application in human stroke ⁸³.

3. Strategies for Improving the Intranasal Insulin Therapy

a) Overview of Advantages and Challenges

Intranasal insulin administration results in direct transport of insulin from the nasal cavity to the CNS via intra-neuronal and extra-neuronal pathways that bypass the blood-brain barrier and minimize systemic side effects ¹². Therefore, a major advantage of intranasal delivery is that it offers the potential for unrestricted transfer of therapeutic compounds to the brain or

CSF, enabling higher local levels to be achieved for disease-specific targeting⁸⁴. For example, intranasal insulin administration increases CSF levels of insulin^{58, 70}, is safe in humans^{58, 85}, and avoids repeated injections. Nonetheless, challenges exist with respect to the eventual broadened use of intranasal therapy. The major ones include: 1) inaccurate delivery and dosing by older adults; 2) the need to improve drug stabilization and time- and dose-regulated release; 3) transport and penetration across the nasal mucosa; 4) nasal transport “resistance”; and 5) CNS versus systemic targeting.

b) Challenges pertaining to accuracy of delivery and dosing

Delivery of intranasal insulin can prove challenging for older adults. One concern is that the dosing may be inaccurate due to failure to deliver the insulin to the olfactory system and cerebrospinal fluid rather than the respiratory or gastrointestinal tract. Therefore, there is a need to optimize intranasal insulin delivery systems to produce more consistent therapeutic effects. To this end, preclinical and human studies examined the effects of incorporating insulin into hydroxypropyl gel and installing it into the nasal cavity with a bio-adhesive compound. This approach proved successful for the release of insulin but was associated with sharp declines in blood sugar⁸⁶. Continued modification of related technologies designed to achieve consistent and predictable effects on hyperglycemia holds promise for the treatment of diabetes mellitus. However, the studies did not provide data on CNS delivery of insulin.

c) Drug Stability and Regulated Release

Challenges pertaining to stability and time course of drug release are being addressed through the use of polysaccharide nanoparticles and hybrid polysaccharide/oligosaccharide nanoparticles as carriers for macromolecules. For example, insulin-loaded chitosan (CS) and cyclodextrin (CD) derivative-based nanoparticles were shown to effectively reduce plasma glucose levels⁸⁷. Another approach includes the use of oligo-arginine-linked polymer backbones to insulin to enhance penetration across the nasal mucosa and more effectively achieve therapeutic reductions in plasma glucose⁸⁸. The use of lyophilized nasal insert formulations can extend nasal residence and thereby enable prolonged delivery and avoid the need for repeated use of nasal spray solutions⁸⁹.

d) Transport and Penetration Across Nasal Mucosa

An important challenge posed by intranasal delivery of insulin is that insulin is not well absorbed through the nasal mucosa due to its large size, hydrophilic nature, and low permeability across membranes. This problem exists for macromolecular therapeutics in general⁹⁰. One approach has been to use nanoparticles⁹¹, but research along these lines has not yet reached fruition. Another approach involves the administration of tetradecyl-beta-D-maltoside (TDM), which has been shown experimentally to improve recovery of nasal permeability barrier following repeated intranasal administrations of peptides⁹². Further research and development is needed to: 1) improve intranasal absorption of compounds; 2) optimize bio-adhesive delivery systems for sustained and controlled drug delivery; and 3) expand the use of water soluble powders to extend shelf-life and transportability of compounds intended for intranasal therapy⁹³.

e) Nasal Transport “Resistance”

Another challenge confronting the chronic use of intranasal insulin and other drug deliveries is the development of time-dependent reductions in nasal permeability. This form of nasal transport resistance is caused by alterations in nasal morphology due to loss of cell-to-cell junctions⁹². Therefore, specific strategies are needed to facilitate transport of various compounds across the nasal epithelium, and thereby maintain the effectiveness of intranasal therapy in chronic use settings. To this end, investigators examined the effectiveness of cyclopentadecalactone (CPE-215), a compound that enhances absorption of molecules across mucous membranes, for intranasal insulin delivery (Nasulin, CPEX Pharmaceuticals). In a clinical trial, the investigators demonstrated that a nasal spray containing recombinant human insulin with CPE-215 could effectively lower blood glucose in diabetics, such that the dose-response pharmacodynamics were proportional and linear^{94, 95}.

f) CNS Versus Systemic Targeting-Resolving Therapeutic Objectives

Confusion over the therapeutic applications of intranasal insulin exists because the objectives differ among groups. Investigators fall into two dominant groups: those intending to treat diabetes mellitus by producing consistent therapeutic levels of plasma insulin, and those interested in restoring insulin responsiveness in states of brain insulin resistance/deficiency associated with MCI, AD, or obesity⁹⁶. For example, in a clinical study of healthy individuals, delivery of intranasal insulin using CPE-215 technology produced peak plasma levels of insulin 10 to 20 min. later, and persistence of elevated plasma insulin for approximately one hour. Correspondingly, plasma glucose levels declined in an insulin dose-dependent manner, but self-corrected within 1.5 to 2 hours of treatment⁹⁷. The results of similarly focused studies advocate the use of intranasal delivery systems to control hyperglycemia safely.

In contrast, in a separate publication, the investigators emphasized insulin-stimulated alterations in hypothalamic activity that regulates homeostatic and reward-related functions, and pointed out that changes in peripheral insulin resistance were short-term (30–120 min later) following intranasal administration⁷³. Furthermore, intranasal insulin was deemed attractive for treating aging populations with cognitive impairment or early AD because insulin is directed to the brain and CSF and has minimal systemic absorption. Moreover, clinical studies have shown that intranasal insulin improves memory⁹⁸. In essence, at the core of the problem is the fact that using essentially the same tools, the brain-focused studies boast of the robust CNS and limited systemic responses, while the diabetes-focused studies omit data about CNS effects. Going forward, more attention should be paid to the pharmacodynamics of intranasal therapy and perhaps the approaches could be tailored to favor CNS or systemic delivery. One example of success along these lines pertains to the use of the rapidly acting insulin analog, insulin Aspart, which when administered intranasal, enhances memory without altering plasma insulin and glucose levels⁹⁹. However, further research is needed to determine the degree to which different formulations of insulin designed for intranasal delivery are free of systemic actions.

4. Adverse Effects

Intranasal insulin therapy can produce unwanted systemic effects including hypoglycemia and elevated blood pressure. In one clinical study, repeated intranasal administration of insulin, every 10 minutes for 2 hours, caused immediate increases in diastolic, systolic, and mean arterial blood pressure¹⁰⁰, which, in the acute setting, could be concerning for individuals with hypertension. However, since these elevated blood pressure responses are not prolonged, chronic intranasal insulin administration should not be regarded as unsafe¹⁰⁰. Another potential adverse effect of intranasal insulin is excessive delivery with production of high local CNS levels. Since high levels of insulin can be injurious and promote tissue degeneration^{101–105}, strategies must be taken to ensure that the dosing rates and levels are optimized (see Expert Opinion below). Finally, as insulin has growth promoting properties, prolonged use may “encourage” proliferation of neoplastic cells¹⁰⁶.

5. Alternative Approaches

Alternative approaches previously considered for treating or preventing AD include the use of insulin sensitizer such as thiazolidinediones and sulfonylurea. Thiazolidinediones function by enhancing insulin sensitivity whereas sulfonylurea increases peripheral insulin concentrations⁹⁸. In a retrospective case-control study, no significant alterations in risk for developing AD were associated with long-term treatment of diabetes mellitus with sulfonylureas, thiazolidinediones, or insulin¹⁰⁷. However, the data are difficult to interpret because of the non-random approaches to treatment and different cross-sectional outcomes of diabetes.

Initial small-scale, short-term Phase II clinical trials suggested that treatment with rosiglitazone, a gamma peroxisome-proliferator activated receptor (PPAR) agonist, could effectively delay progression of cognitive impairment by preserving attention and memory functions and maintaining amyloid-beta clearance rates in subjects with MCI or early AD¹⁰⁸. Others found similar results but the benefits were mainly observed in individuals who had APOE-E4-negative genotypes^{109,110}. Similarly, the efficacy of rosiglitazone for treating AD-type neurodegeneration was also demonstrated in standard mouse models^{111,112}. However, in Phase III placebo-controlled, randomized-clinical trials that were stratified with respect to APOE-genotype, no significant long-term benefit was observed for rosiglitazone monotherapy versus placebo^{113,114}, or when combined with an acetylcholine esterase inhibitor¹¹⁵. Small scale studies with pioglitazone, another gamma PPAR agonist drug, have also not produced convincing therapeutic responses^{116,117}.

Results from the most rigorously conducted clinical and pre-clinical studies suggest that insulin sensitizer drugs, including PPAR agonists, produce no significant long-term therapeutic effects and do not halt progression of dementia in mild or moderate AD. Yet, in the short-term studies or early phases of long-term studies, positive effects of rosiglitazone were measured. In addition, in an experimental model of AD produced by treatment with a pro-diabetes toxin, both delta and gamma PPAR agonists were effective in preserving learning, memory, and hippocampal structure⁴². In light of the full discussion included in this work, particularly the need to better target CNS insulin resistance by intranasal delivery,

future drug designs should entertain the concept that brain insulin resistance disease states might be effectively treated with CNS-specific PPAR agonists or other classes of insulin sensitizers delivered via the intranasal route.

6. Conclusions

Intranasal insulin therapy holds promise for targeting brain insulin resistance associated with cognitive impairment and neurodegeneration, including AD, due to its ability to enhance and preserve memory and relatively high safety index. Since intranasal insulin also can be used to treat systemic insulin resistance diseases, mechanisms to ensure CNS versus systemic delivery/transfer are needed. Compounds other than insulin may be delivered via the intranasal route to treat a range of CNS diseases. Technical barriers pertaining to stability, rate of delivery, and transport across nasal epithelium must be overcome to optimize intranasal insulin therapy for chronic diseases.

7. Expert Opinion

While intranasal therapy is a very promising approach for the treatment of CNS diseases due to better targeting and ability to by-pass the blood-brain barrier, the methods and reagents employed from study to study are not identical. Standardized approaches that preferentially result in delivery of compounds to the CNS rather than periphery, and vice versa are needed. As the field moves forward, consideration should be given to developing compounds that regulate the rate, timing, and levels of insulin release, perhaps through the use of nanotechnology. The need to refine the parameters of intranasal insulin delivery is particularly relevant to its long-term use as the therapeutic efficacy may vary with the patient's age, stage of cognitive impairment, and time span of treatment. Elderly patients may require tight regulation of insulin release to prevent surges and attendant side effects. At the same time, mechanisms to provide as-needed pulsatile delivery of insulin could be advantageous for accommodating the so-called 'bad days' of dementia and helping to quickly restore mental clarity, particularly when important decisions are needed. With long-term use of intranasal insulin, adjustments to dosing and timing will be needed. Therefore, delivery agents should be improved to accommodate changes in treatment requirements.

There is a need to monitor the efficiency and distribution of CNS insulin and other drugs delivered via the intranasal route. In particular, more sensitive approaches for in vivo imaging of compounds, their metabolites, and effects should be developed. Currently, studies designed to examine the effectiveness of intranasal therapy rely in neurocognitive testing or neuro-imaging techniques such as fMRI or PET scanning. However, besides evaluating the consequences of intranasal insulin delivery, more information is needed about CNS localizations of the compounds, their half-lives in different brain regions, and the changes in those parameters over time. Since dementia is not a static process and over time, neurodegeneration worsens and gradually affects a broader range of brain structures, determining if the insulin or other treatments reach the additional targets will be important for evaluating efficacy. Discordances between delivery and metabolism would raise concerns about brain region-specific emergence of insulin resistance which would have to be overcome, possibly by alternative therapeutic measures.

As it is evident that neurodegeneration, including Alzheimer's disease, is mediated by a multi-step and multi-pronged cascade, most likely effective treatment will require more than a single agent and will likely change with disease progression. Therefore, the scope of therapeutic compounds that could be delivered effectively to the brain via the intranasal route should be broadened. Besides improving means of measuring uptake and delivery to the brain as discussed above, further research should determine if the administration of more than a single compound is feasible and the extents to which interferences or facilitated deliveries occur. In addition, the development of in vivo imaging approaches to assess pharmacokinetics of multiple compounds will be needed. Similar approaches could be utilized for CNS targeted treatment of primary brain neoplasms, epilepsy, and infarcts (strokes).

As with many receptor-mediated therapeutic agents, over time, cellular adaptations can lead to relative resistance and reduced efficacy of the compounds. Long-term studies are needed to assess tolerance to intranasal insulin therapy, and further the understand mechanisms for over-coming this problem, as well as predicting host susceptibility to this adaptive response. Alternatively, receptor resistance could reflect disease progression. The ability to distinguish adaptive from disease related receptor resistance is important because the corrective measures could differ. For adaptive receptor resistance, efforts should be made to develop approaches to “refresh” receptor or prevent their “exhaustion” by devising other means of drug delivery, perhaps via alternate receptors or receptor-independent mechanisms. For disease-mediated receptor resistance, which could be caused by deterioration of downstream signal transduction pathways, alternative therapeutic measures would have to be implemented to overcome the fundamental problems caused by impaired insulin signaling. For examples, effective insulin sensitizer agents that function at the level of the nucleus can drive metabolic functions, yet bypass the need for upstream activation of insulin receptors.

Since Alzheimer's and other neurodegenerative diseases are progressive, their pathologic and pathophysiologic features change over time, producing additional potential targets for therapy. As is the case for most malignancies, which are seldom cured with a single drug, with the advancement of neurodegeneration, multi-pronged therapeutic approaches will be needed to extend the benefits of intranasal insulin. The types of treatments that are needed are directly related to the consequences of insulin resistance, e.g. oxidative and endoplasmic reticulum stress, metabolic dysfunction, neuro-inflammation, impaired neuronal plasticity, and cell death. With regard to neuronal plasticity, it should be possible to supply neurotrophins via the intranasal route, but their efficacy for treating cognitive impairment and neurodegeneration requires further study. Intranasal delivery of peptides to the brain is preferred because of their high likelihood of degrading after oral administration, and inefficiently entering the CNS after parenteral administration. In contrast, treatment of other aspects of neurodegeneration may be accomplished by administering the drugs through other routes, particularly if they have not yet been adapted for intranasal delivery. The challenge will be to identify which classes of additional and alternative therapeutic compounds are needed and once administered, determining their specific effectiveness. This concept rests on developing newer approaches for assessing pathologic consequences of brain insulin deficiency and resistance that mediate progressive neurodegeneration.

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Article highlights

- In the normal brain, insulin signaling has diverse and critical functions including neuronal survival, metabolism, and plasticity.
- Brain insulin resistance mediates cognitive impairment in neurodegeneration, including Alzheimer's disease, as well as in obesity and diabetes.
- Intranasal insulin is as effective as systemic insulin treatment, but avoids the need for repeated injections, and with respect to the brain, the approach can lead to preferential targeting of CNS diseases with minimal unwanted systemic responses.
- Intranasal insulin has proven effects in slowing progression of cognitive impairment and Alzheimer's disease.
- Intranasal insulin has positive therapeutic effects on brain functions pertaining to food intake and satiety, and therefore could be optimized for use in treatment programs for obesity.
- Alternative approaches for treating CNS insulin resistance, including the use of insulin sensitizers, were met with initial positive results in short-term studies, but failed to show significant benefits in long-term studies. Although this approach has fallen out of favor, the problems encountered in later clinical trials could have been due to inadequate brain targeting with attendant systemic side-effects, and use of selected compounds that were not brain-specific.