REVIEW

Intranasal Insulin: a Treatment Strategy for Addiction

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Abstract

Addiction to substances such as alcohol, cocaine, opioids, and methamphetamine poses a continuing clinical and public challenge globally. Despite progress in understanding substance use disorders, challenges remain in their treatment. Some of these challenges include limited ability of therapeutics to reach the brain (blood–brain barrier), adverse systemic side effects of current medications, and importantly key aspects of addiction not addressed by currently available treatments (such as cognitive impairment). Inability to sustain abstinence or seek treatment due to cognitive deficits such as poor decision-making and impulsivity is known to cause poor treatment outcomes. In this review, we provide an evidenced-based rationale for intranasal drug delivery as a viable and safe treatment modality to bypass the blood–brain barrier and target insulin to the brain to improve the treatment of addiction. Intranasal insulin with improvement of brain cell energy and glucose metabolism, stress hormone reduction, and improved monoamine transmission may be an ideal approach for treating multiple domains of addiction including memory and impulsivity. This may provide additional benefits to enhance current treatment approaches.

Key words Nose-to-brain delivery · hypometabolism · alcohol use disorder · cortisol

Introduction

Addiction to substances such as alcohol, cocaine, opioids, and methamphetamine poses a continuing clinical and public challenge globally. In the United States, 25% of adults report binge alcohol consumption, and 7% (nearly 17 million) are diagnosed with alcohol use disorders [1]. Although the reported numbers are smaller for other substance use, they result in increased healthcare costs, utilization, and adverse health outcomes [1]. In the last 15–20 years, there is a better understanding of the pathological changes within the brain and its circuitry that promote substance abuse. However, challenges remain in the treatment of drug addiction that can potentially be addressed by novel approaches such as intranasal drug delivery, specifically intranasal insulin as discussed here.

Currently, pharmacotherapy exists only for alcohol use disorders (AUD) and opioid addiction, but has several limitations including multiple adverse effects, compliance with dosing regimen, availability/access, and utilization of treatment [2–12]. A comprehensive review of the current treatment for drug addiction is beyond the scope of this review. Briefly, focus of treatment is largely dependent on managing withdrawal symptoms, psychotherapy, and support groups. Pharmacotherapy for AUD (FDA approved) includes disulfuram, naltrexone, nalmefene, and acamprosate and a few non-FDA-approved treatments such as topiramate, baclofen, or gabapentin [2, 3]. Despite extensive research, there are currently no effective pharmacological based treatments for other addictive substances, including psychoactive stimulants (cocaine, methamphetamines), marijuana or synthetic cannabinoids, hallucinogens, phencyclidine (PCP), or drugs such as methylenedioxymethamphetamine (MDMA) [13, 14].

Limitations to pharmacotherapy include treatment under supervision, aversive reaction (disulfiram), precipitation of opioid withdrawal in opioid users (naltrexone), dosing regimen compliance (acamprosate), specialized treatment (topiramate), and multiple side effects, with some serious outcomes. Opioid addiction is commonly treated with methadone and buprenorphine [2]. Methadone is associated with multiple adverse outcomes including constipation, respiratory depression, and heart rhythm abnormalities, whereas buprenorphine

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can precipitate opioid withdrawal [2]. Another important limitation for an effective treatment is the blood–brain barrier (BBB). The BBB severely limits the therapeutics that can be used and use of high doses to overcome the BBB can lead to systemic side effects.

Multiple aspects of both acute and long-term management are neither targeted nor addressed by currently available pharmacological and non-pharmacological therapies [10]. Recent articles suggest that across all substance use disorders (SUD), cognitive deficits exist that are known to predict treatment response and sustained abstinence [14–18]. Most commonly encountered cognitive deficits include impaired or poor decision-making ability, impulsivity, impaired cognitive flexibility, deficits in learning and memory, and heightened attention to drug-associated cues [14, 15]. In addition, both addicts in abstinence with cognitive deficits and people with mood disorders are at higher risk of substance use or relapse [16–18]. This suggests that for a favorable outcome of treatment or prevention of relapse or maintenance of abstinence, it is essential to treat cognitive and behavioral deficits. We present the rationale for using intranasal insulin, which has the potential to treat multiple targets within the brain including cognitive deficits and to address key limitations and challenges currently faced in the treatment of addiction.

Intranasal Drug Delivery

In 1989, William Frey II filed the first patent on his discovery of the intranasal delivery method, which bypasses the BBB to target therapeutics (including insulin) to the brain to treat brain disorders including Alzheimer's disease and stroke [19–22]. Subsequently, William Frey II received an additional patent on the specific use of intranasal insulin to treat Alzheimer's disease and Parkinson's disease [23, 24].

Since its discovery, intranasal delivery of drugs to the central nervous system (CNS) has been successfully demonstrated by numerous researchers worldwide, resulting in many publications. Intranasal delivery has been studied extensively with regard to mechanism of transport to the brain. Intranasal therapeutics reach the CNS within minutes via extracellular mechanisms including perineural and perivascular transport [22, 25–34]. Intranasal drug delivery to the brain is dependent on extracellular convection or bulk flow along the olfactory and trigeminal neural pathways whereas delivery throughout the brain involves passage through the perivascular spaces of the cerebrovascular system on the brain side of the BBB [35]. Intranasal insulin can be found in the cerebrospinal fluid in humans 10 min after administration [27]. It is not essential that drugs be modified for intranasal drug delivery to the CNS. Key advantages of intranasal delivery include allowing for direct delivery of large and/or charged therapeutics to the CNS from the nasal mucosa while reducing systemic exposure

and adverse side effects for multiple brain therapeutics including those that cross the BBB. In addition to peptides [36, 37], such as insulin, charged small molecules [38], adeno-associated virus gene therapy [39], therapeutic cells including stem cells [40, 41], T cells [42], macrophages, and microglia [43] have all been delivered to the brain to treat CNS disorders. Multiple intranasal therapeutics for treating brain disorders have been developed [44–56], but this review focuses on restoring brain cell energy and metabolism, and other actions of intranasal insulin that can potentially be beneficial for the treatment of addiction.

Intranasal Insulin

The use of intranasal insulin administration to non-invasively deliver and target insulin to the brain could lead to advancements in treatment for addiction. The intranasal insulin treatment has been shown in multiple human clinical trials to safely improve memory, attention, and functioning in patients with mild cognitive impairment (MCI) or Alzheimer's disease (AD), to improve memory, motor symptoms in patients with Parkinson (PD), to improve memory in adults with type 2 diabetes, and even to improve memory in normal healthy adults [57–70]. In addition, intranasal insulin has been studied with regard to food/eating behavior, diabetes (insulin resistance), stress axis, and sleep [71–79].

Study of the pharmacokinetics of intranasal insulin in mice showed only 3% of intranasal insulin entered the circulation and no peripheral metabolic effects were detected up to a day after intranasal administration [80]. A single intranasal dose of 40 IU insulin induces an increase in the cerebrospinal fluid concentration of insulin distinctly above the normal level in healthy individuals [27]. A recent review of safety of intranasal human insulin trials revealed no safety concerns, with no serious adverse events or symptomatic hypoglycemia in a total of 1092 individuals studied [81]. Though some studies with higher doses (160 IU) have shown small detectable increase in insulin levels, no significant change in blood glucose levels were noted [82].

Insulin and Substance Use Disorders

Multiple reviews by Koob and colleagues over the years have provided extensive evidence for involvement of multiple neurotransmitter systems and brain areas involved in development, and evolution of different phases of the addiction cycle [83–89]. Different classes of drugs are associated with dysfunctions in a range of overlapping brain regions including midbrain dopamine pathways (ventral tegmental area [VTA], substantia nigra [SN]), basal ganglia (ventral striatum, nucleus accumbens [NAcc], and dorsal striatum) prefrontal cortex ([PFC]; dorsolateral prefrontal cortex [DLPFC], ventromedial prefrontal cortex [vmPFC]), cingulate cortex, hippocampus,

inferior frontal gyrus, insula, amygdala, and cerebellum involved in drug reward, emotion, cognition, and behavior.

Insulin signaling has been determined to be instrumental in the overall health and function of the central nervous system (CNS) [59, 90]. Studies have demonstrated that insulin and insulin receptors (IR) are expressed widely within the brain as in peripheral tissues [91, 92]. Insulin levels in the brain when compared to plasma can reach 10 to 100 times higher, especially in hippocampus, hypothalamus, cortex, olfactory bulb, substantia nigra, and pituitary [92, 93]. Briefly, insulin binds to the insulin receptor (IR) resulting in the phosphorylation of insulin receptor substrate (IRS) resulting in activation of two signaling pathways (phosphatidylinositol 3-kinase [PI3K]-AKT/protein kinase B [PKB] and Ras-mitogen-activated protein kinase [MAPK] pathways) known to play pivotal roles in normal brain function. Beginning from insulin levels in the periphery to specific molecular and cellular targets within the brain, impairments occur and span across different stages of the addiction cycle. Specifically relevant to this review, we discuss the current evidence for impaired insulin signaling in SUD.

Reward and Habit Formation

The mesolimbic dopamine system (VTA, striatum) is generally considered the most important mediator of drug reward and appears to be common to both acute and chronic effects of SUD [83].

Dopamine Neurotransmission

Dopamine transporter (DAT), an enzyme associated with clearing of extracellular DA, is a major target of substance use (cocaine, amphetamine) associated with stimulant actions. Insulin has been shown to increase DAT expression, suggesting a key role in mediating the cognitive and motivational effects [94–100]. Pre-clinical studies in animals and tissue cultures suggest that persistent DAT function at DA nerve terminals in striatum are due to activation of IRs, through stimulation of the PI3K pathway [96, 97, 101]. In addition, insulin modulates the pre-synaptic transporters sensitive to cocaine in nucleus accumbens (NAcc) suggesting a target for treatment of impulsivity in these patients [102]. In humans, Akt has been found to be associated with MA abuse and associated dysregulation of the DA system [103, 104]. Moreover, the insulin functions mentioned above suggest a potential relationship between addiction and food intake processes associated with DA neurotransmission and its pathway [98, 105–107]. Application of insulin at the VTA reduces food intake and consumption of high fat food, presumably affecting the DA neurocircuitry [108–110].

Currently, multiple studies have targeted these mechanisms using intranasal insulin in studying eating or food-related behaviors. Intranasal insulin has been shown to reduce food intake in adult men [111] and snacks in women if given in a suitable time window [73]. Tiedemann and colleagues [78] used intranasal insulin to demonstrate the link between feeding systems, and modulation of mesolimbic pathways by insulin with regard to food stimuli in humans. Thanarajah and colleagues in 2019 [60] report the pharmacokinetics of intranasal insulin and dose dependency of its modulatory effects on the midbrain. Key findings of this study suggest that insulin regulates feeding behavior through its action on midbrain dopamine neurons and the ensuing consequences for reward-related and motivational processes [110, 112]. With similar mechanisms between SUD and impaired feeding systems, a recent study shows the promise of intranasal insulin for SUD. Briefly, Naef et al. studied the effects of intranasal insulin along with intra-VTA insulin in rats and showed that DA in NAc was suppressed by insulin and blocked by an insulin receptor antagonist suggesting suppression of attention to drug related cues with cocaine [113].

Insulin Signaling

Apart from DA in the VTA, insulin is thought to act on multiple targets through its downstream effects of signaling in the CNS. For example, in long-term opioid (morphine) users, decreased levels of insulin growth factor-1 (IGF-1) and insulin receptor substrate (IRS) proteins have been demonstrated in the VTA [114, 115]. Studies in Drosophila of mutations of insulin-like peptides showed that insulin signaling is involved with toxic effects of alcohol by potentially engaging insulin signal transduction mechanisms [116]. Similarly, the disruption of the phosphatidylinositol-3 kinase (PI3K) cascade in the VTA by a dominant negative insulin receptor substrate 2 (IRS2) protein attenuates the rewarding properties of cocaine and morphine in rodents [117, 118]. Animal studies with repeated administration of methamphetamine also showed effects on insulin signaling due to impaired expression of multiple components of insulin signaling such as IRs, PI3K and glycogen synthase kinase 3-beta (GSK3β) [119, 120]. Overall, the studies mentioned above suggest the potential use of intranasal insulin to address impaired insulin signaling in the brain.

Other Neurotransmitters

Along with DA, multiple neurotransmitters are involved in mediating the drug reward effects in SUDs. Independent neurotransmission involving the opioid peptides, GABA, and endocannabinoids are known to affect the mesolimbic system [84, 88]. Insulin is also known to modulate the effect of a number of these neurotransmitters such as GABA by activating synaptic IR and may reduce symptoms in depression and sleep regulation [121–125]. In addition, insulin induced long-

term depression (LTD) of AMPA-mediated excitatory post-synaptic transmission by synthesis of endocannabinoids, and glutamate release onto VTA dopamine neurons [126, 127]. Although this shows the potential of insulin affecting these systems, further studies are required to establish the interplay with insulin signaling, especially in the midbrain.

Cognition and Behavior

Neurocognitive impairments are common to all SUD [128, 129]. Cocaine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and nicotine are associated with neurocognitive changes including learning and working memory deficits with acute or chronic exposure, present during abstinence [130–137] and associated with poor treatment outcomes. It is hypothesized that pre-existing working memory deficits increase vulnerability to drug addiction [14]. In AUD, deficits are observed in executive functioning (such as abstract reasoning, problem solving skills, and cognitive flexibility), visuospatial abilities, and perceptual-motor integration, and these deficits are persistent beyond several weeks of abstinence (45%) or a year of abstinence (15%; [138–141]). In the sections below, we discuss mechanisms known to be involved in SUD which may possibly be improved with intranasal insulin.

Cerebral Hypometabolism

Cerebral hypometabolism with reduced glucose uptake and related neuro-structural changes are key factors involved in acute and long-term cognitive impairment or deficits in individuals with SUD, including AUD. Preclinical studies in animals undergoing withdrawal after chronic extended access to cocaine showed decreased glucose utilization of brain regions involved in learning and memory such as the PFC, hippocampus, and striatum [142]. Significant reduction of glucose utilization in some of these regions lasts longer and may facilitate continued drug use even if associated with tolerance and negative effects. Moreover, consistent with human studies, animals with impaired memory showed significantly higher seeking behavior for drugs than do controls. For example, neonatal ventral hippocampal lesions in rats, which lead to working memory deficits, resulted in increased reinstatement of nicotine seeking [143]. In addition, chronic exposure to nicotine, methamphetamine, and cocaine, or cocaine withdrawal resulted in changes in neurogenesis in the hippocampus [144–148].

In 1966, Roach and colleagues provide the initial suggestion that impaired glucose metabolism may be an underlying cause for alcoholism [149]. Decades later, brain imaging studies have shown reduced glucose utilization by the brain, in both resting and sensory stimulation during acute alcohol administration, including with low doses of alcohol in humans ((with or without behavioral abnormalities) [89, 150–158]).

Studies using ^{18}F-2-fluoro-deoxy-glucose (FDG)-positron emission topography (PET) in patients with AUD show that there is 20% global reduction in glucose uptake [159], similar to results in neurologically intact patients with AUD [152, 155]. In addition, regional changes in hypometabolism were observed in the frontal cortex including the anterior cingulate cortex (ACC) when compared to controls [159–162]. Regional changes in hypometabolism have been suggested to be linked to cognitive dysfunction, as reduced frontal and anterior cingulate metabolism are reported to correlate with mental control, category subset scores [155, 161], four-dimensional neurocognitive model (verbal memory, visual memory, verbal knowledge, and attention/executive functioning, [163]) and Wisconsin Card Sorting Test scores in alcoholics respectively [139, 164]. To further elucidate changes in glucose metabolism in AUD, Ritz et al. showed grey matter shrinkage and hypometabolism in the fronto-cerebellar circuit and several nodes of Papez's circuit, along with some regions showing disproportionate increase in hypometabolism when compared to grey matter shrinkage [165]. In addition, AUD with Korsakoff's syndrome results in cerebral glucose hypometabolism with particular severity in the middle cingulate cortex [166]. AUD is frequently associated with anxiety and depression. Clinical studies have shown altered posterior cingulate cortex functions in patients with mood disorders, including decreases in cerebral glucose metabolism [167, 168] and activation during emotional processing [169], relative to healthy controls.

Insulin and insulin signaling transduction play a key role in modulating cognition. Central insulin and IRs have been established as differing from that of the systemically occurring counter parts that specifically regulate glucose utilization. Energy metabolism in the CNS is largely dependent on glucose uptake and its utilization. Glucose metabolism is essential for both neuronal and non-neuronal physiological functions, regulation of cerebral blood flow, cell death pathways, and neurotransmitter synthesis [170]. Although there are multiple regulators of glucose metabolism in CNS [170], one of the key regulators is insulin, especially in certain brain regions.

In rodents, IRs and insulin-sensitive glucose transporters are selectively co-localized in brain areas responsible for memory, thus providing a platform for insulin signaling whereby selective increases in cerebral glucose utilization could modulate memory [171]. Consistent with evidence of insulin functioning as a neuromodulator for memory-related function is the high density of IRs in the hippocampus and cerebral cortex, brain regions integral to the formation, retention, and recall of information [90, 172]. Systems with impaired insulin signaling pathways have demonstrated inhibition of acetylcholine biosynthesis and subsequently have incurred debilitating effects on neuronal plasticity [173, 174]. Increased insulin resistance and glucose intolerance has been

observed in a multitude of neurodegenerative processes including Alzheimer's disease [175], Parkinson's disease [176], and Huntington's disease [177] suggesting a common pathway.

Intranasal insulin in animal studies using Alzheimer's and Parkinson's disease models has been shown to improve cognitive function [178] [179] [80]. Fluorodeoxyglucose (FDG)-PET imaging studies have demonstrated a reduction in the loss of glucose uptake and utilization after intranasal insulin treatment in patients with AD or amnestic MCI in the bilateral frontal, right temporal, bilateral occipital, and right precuneus and cuneus regions of the brain [63]. Specifically, clinical trials with intranasal insulin (both short and long term) in memory-impaired subjects (AD, MCI) have shown improvement in declarative memory tasks [70], greater story recall, improved word list recall with sustained benefit (21 day treatment) [180], and improved delayed memory during a 4-month treatment trial [63]. Improvement of cognitive function including glucose uptake and metabolism suggests that intranasal insulin may provide an opportunity to target specific cognitive deficits that may improve long-term outcomes with SUD. In support are the recent studies with intranasal insulin showing improvement in cognitive impairments and craving associated with addiction in smokers [181–183].

Stress and HPA Axis

Stress is an important trigger of relapse, and the brain systems that respond to stressful stimuli are thought to be important in maintaining the addicted state. Animal studies suggest activation of the stress/aversion systems (hypothalamic-pituitary axis [HPA], corticotrophin releasing factor [CRF], and dynorphin) and impairment of anti-stress systems (neuropeptide Y) are associated with chronic drug relapse [83, 85, 88, 184]. Insulin is a known actor in HPA axis regulation by binding to IR in hypothalamus, hippocampus, and amygdala [112, 185–189]. Studies in humans suggest central insulin causes reduction in morning HPA axis activity and effectively lowers psychological stress induced HPA axis response by reduction in the level of cortisol [69, 190, 191]. Moreover, the insulin HPA axis response may be related to regulation of the arcuate nucleus of the hypothalamus, including its effects on energy homeostasis [192–194].

Intranasal insulin has been shown to attenuate the HPA axis and reduce cortisol in adult men exposed to stress [190], which is significant as cortisol blocks glucose uptake into the hippocampus [195]. In addition, intranasal insulin has been discussed as a potential intervention to ameliorate post-traumatic stress disorder (PTSD) [47]. Collectively, these studies provide rationale for testing intranasal insulin as a viable therapeutic in extending drug abstinence or reducing episodes of drug relapse in SUD.

Neurogenesis

Hippocampus is a key brain region involved in learning and memory. Impairment of hippocampal neurogenesis has been associated with cognitive deficits in neurodegenerative disorders including AD [196, 197]. Multiple animal and clinical studies in addiction and other psychiatric disorders, such as depression and schizophrenia, suggest that altered hippocampal neurogenesis is a key contributor of these complex clinical disorders [198–200]. Similarly, it is thought that a persistent decrease in hippocampal neurogenesis may increase susceptibility to engage in and maintain drug-seeking behaviors [201]. Briefly, self-administration studies of drugs have shown that reduced hippocampal neurogenesis is associated with increased drug taking and drug-seeking behavior, whereas increasing neurogenesis by exercise or treatment with anti-depressants reduces drug-taking and drug-seeking behaviors [199, 200]. The insulin signaling cascade plays a key role within the hippocampus. Insulin, insulin-like growth factors, IRs, and downstream activation of PI3 kinase and GSK3β are key players in dendritic sprouting, neuronal stem cell activation, cell growth, repair, synaptic maintenance, and neuroprotection [173, 175, 202–204]. Specifically within the hippocampus, insulin facilitates neuronal plasticity by modulating long-term potentiation or long-term depression at synapses [205]. These effects are mediated by PI3 kinase by modulating expression of glutamate receptors including AMPA and NMDA [206]. Further studies are required to elucidate the role of insulin signaling in SUD within the hippocampus.

Preclinical and neuroimaging evidence suggest involvement of PFC and its circuitry in direct effects of drugs, craving, response to cues, inhibitory control, and reward-based decision-making. Using multiple approaches including intranasal insulin, all the PFC regions have been shown to be sensitive to changes in response to insulin, suggesting that insulin signaling may play a role with regard to craving and response to cues in SUDs [75, 82, 207, 208]. This speculation arises from studies using intranasal insulin showing reduced food intake by a) decreased response of the PFC to food cues [208] and a decrease in orbitofrontal cortex resting state activity [75]; b) increasing brain cell energy (ATP and phosphocreatine) using phosphorus-31-magnetic resonance imaging [209].

In summary, studies presented here suggest that insulin is a key modulator in all SUD and targets multiple mechanisms specifically energy metabolism, glucose uptake, neurotransmission, synaptic plasticity, and HPA axis regulation. This suggests that intranasal insulin could play a significant role in the treatment of addiction and associated cognitive deficits in SUD.

Future of Treatment in Addiction—Intranasal Insulin

Intranasal insulin offers an exciting and viable approach to addressing some of the key aspects of SUD, including improving rates of treatment use due to its ease of use and safety. As described in the sections above, intranasal insulin treatment for cerebral glucose hypometabolism has been studied in multiple clinical trials, and benefits related to cognitive and memory impairments have been reported. In summary, intranasal insulin studies show that it 1) safely improves memory in normal healthy adults and in patients with mild cognitive impairment or Alzheimer's disease; 2) reduces cerebral glucose hypometabolism in patients with AD; 3) increases both brain cell energy, ATP, and phosphocreatine in normal healthy adults; 4) attenuates the HPA axis and cortisol response to psychosocial stress in healthy adults; and 5) can be safely tested in patients. The safety and efficacy of intranasal insulin to improve memory, executive functions, drug-seeking behaviors, and control impulsivity in individuals with SUD needs to be assessed in clinical trials.

According to the 2015 National Survey on Drug Use and Health (NSDUH), of the 20.8 million people aged 12 or older who had a SUD during the past year, about 2.7 million (13 percent) had both an alcohol use and an illicit drug use disorder, and 41.2 percent also had a mental illness. With this significant level of polysubstance use, it is important to focus on therapeutics such as intranasal insulin that may provide a practical strategy to improve the treatment of multiple SUD [210].

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest. Although two authors LH and WF are listed inventors on patents related to intranasal Insulin, owned by their non-profit employer, none of these patents are related to the treatment of addiction.

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