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No effect of adjunctive, repeated dose intranasal insulin treatment on psychopathology and cognition in patients with schizophrenia

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Abstract

Objective—This study examined the effect of adjunctive intranasal insulin therapy on psychopathology and cognition in patients with schizophrenia.

Methods—Each subject had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and been on stable antipsychotics for at least one month. In an 8-week randomized, double blind, placebo controlled study, subjects received either intranasal insulin (40 IU 4 times per day) or placebo. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessment of Negative Symptoms (SANS). A neuropsychological battery was used to assess cognitive performance. The assessment for psychopathology and cognition was conducted at baseline, week 4 and week 8.

Results—A total number of 45 subjects were enrolled in the study (21 in the insulin group, 24 in the placebo group). The mixed model analysis showed that there were no significant differences between the two groups at week 8 on various psychopathology and cognitive measures (p's > 0.1).

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Drs. Liu, Ghebremichael, Cohen, Ongur, and Mr. Hayden report no competing interests.

Conclusion—Adjunctive therapy with intranasal insulin did not seem to be beneficial in improving schizophrenia symptoms or cognition in the present study. The implications for future studies were discussed.

Keywords

intranasal; insulin; schizophrenia; psychopathology; cognition

Introduction

Historically, insulin coma treatment presented one of the first active medical approaches to the management of schizophrenia. It was developed in 1930s by Manfred Sakel and quickly found its way into psychiatric wards all over the world[1]. Numerous observational studies have suggested that insulin therapy was effective especially in reducing positive symptoms such as delusions and hallucinations[2]. The treatment was abandoned on practical grounds, also because of the risk of severe hypoglycemia. Of interest, however, is that current, standard antipsychotic drugs, as well as the uniquely effective antipsychotic drug clozapine, may activate insulin signaling pathways in the brain[3, 4]. These actions may be important in producing the clinical therapeutic effects of antipsychotic drugs.

Several mechanisms are now recognized through which insulin may affect brain function. The insulin-sensitive glucose transporter GLUT4 is expressed in the brain and is co-localized with insulin receptors in the hippocampus and hypothalamus[5, 6]. Changes in central insulin levels may thus affect physiology in these selective brain regions. Insulin also modulates neurotransmitters, such as acetylcholine, norepinephrine, and GABA, which influence learning, memory, arousal state, appetite and mood[7–9].

Recent studies have suggested that insulin may act as a neuromodulator increasing cell membrane expression of N-methyl-D-aspartate (NMDA) receptors[10] and enhancing NMDA receptor activity[11]. Insulin might potentiate the NMDA receptor activity by altering the NMDA receptor's phosphorylation state[12]. NMDA receptor activity is well known to be involved in long-term potentiation and memory[13, 14]. Further, hypofunction of NMDA receptors has been proposed as an important pathophysiological feature of schizophrenia[15]. The NMDA receptor antagonists, such as ketamine or phencyclidine, can reproduce the full range of symptoms as well as the physiological manifestations of schizophrenia such as hypofrontality[16], impaired prepulse inhibition[17] and enhanced subcortical dopamine release[18]. On the other hand, clinical trials with agents (e.g., glycine, D-cycloserine) that enhance NMDA receptor function have shown improved clinical symptoms in patients with schizophrenia[19].

Given the linkage between insulin and its potentiation effect on NMDA receptors, and the role of NMDA receptor hypoactivity in the etiology of schizophrenia, it is speculated that centrally administrated insulin might improve clinical symptoms of schizophrenia through the modulatory effect of insulin on NMDA receptors.

Owing to its high molecular weight and the lack of lipophilicity, intranasally administered insulin has poor systemic absorption[20]. Meaningful metabolic effects after intranasal insulin

administration are recognized only if absorption enhancers are used, and even then large doses of insulin are required[21]. In contrast, intranasal insulin can reach the brain and cerebrospinal fluid via extracellular bulk flow transport along olfactory and trigeminal nerve pathways in addition to axonal transport pathways[22]. In healthy, young adults, intranasal administration of insulin (a single dose of 40 IU) resulted in increased cerebrospinal fluid (CSF) insulin levels within 10 minutes of administration with peak levels noted within 30 minutes[23]. CSF insulin levels had not returned to baseline by the end of the 80 minutes study, while blood glucose and insulin levels did not change. Human studies have demonstrated that intranasally administered insulin does not change systemic blood levels of glucose and insulin; therefore, the risk of hypoglycemia is minimal[23, 24].

Our group previously reported negative findings of single dose intranasal insulin treatment on cognition in patients with schizophrenia[25]. We now present the results of an 8-week, randomized, placebo controlled, double blinded study to examine intranasal insulin's effects on psychopathology and cognition using the Positive and Negative Syndrome Scale (PANSS), the Scale for Assessment of Negative Symptoms (SANS) and a cognitive battery.

Methods

Subjects

Adult outpatients with schizophrenia or schizoaffective disorder were recruited from an urban community mental health clinic. Psychiatric diagnosis was determined using the Structure Clinical Interview for DSM-IV (SCID)[26]. Other inclusion criteria included: 1) age 18 to 65 years; 2) stable dose of the current antipsychotic drug for at least 1 month; 3) English speaking and able to complete the cognitive assessment. Exclusion criteria were: 1) inability to provide informed consent; 2) current substance abuse; 3) unstable medical conditions; 4) diagnosis of diabetes mellitus. The study was approved by the institutional review boards of the Massachusetts General Hospital (MGH) and the Massachusetts Department of Mental Health.

Procedure

At baseline, eligible subjects completed an assessment which included the Positive and Negative Syndrome Scale (PANSS)[27], the Scale for Assessment of Negative Symptoms (SANS)[28], the Calgary Depression Rating Scale[29], the Heinrichs Carpenter Quality of Life Scale (QLS)[30], and the Systematic Assessment for Treatment Emergent Events (SAFTEE)[31]. The SAFTEE assesses 23 categories of possible drug side effects organized according to organ system or body region, with a total of 78 specific queries. In addition, subjects were assessed by a cognitive battery that included: the Verbal Fluency Test, the Trail Making Test, the Digit Span subscale from the Wechsler Adult Intelligence Scale – III (WAIS-III), the Hopkins Verbal Learning Test (HVLT), and the Continuous Performance Test – Identical Pairs (CPT – IP).

After the baseline measures were completed, subjects were instructed how to use the nasal spray device and deliver the study medication properly. Subjects were instructed to administer the study medication 4 times per day. At each time, subjects administered 4 puffs

(0.4 ml) of study medication (alternating between nostrils, 2 puffs per nostril) (either 40 IU insulin or placebo). The total daily dosage was thus 160 IU (1.6 ml). Subjects were instructed to sniff following administration to facilitate the transport of insulin into the nasal cavity.

Subjects were randomized to receive either human regular insulin (Humulin® R, Eli Lilly, IN) or placebo (vehicle without active insulin ingredient), in a double-blinded fashion. Randomization and packaging of study medications were performed by the MGH research pharmacy.

A mechanical multi-dose nasal spray device (Equadel®, Valois of America, NY) prepared with either insulin or placebo was used in this study. The device and procedures used in this study was similar to the devices and procedures used to administer intranasal insulin in published studies, including those that show effects in brain. The nasal spray device was designed to release 0.1 ml per puff containing either 10 IU insulin, or placebo. The nasal actuator was connected to a 30 ml plastic container. The connection between nasal actuator and container was sealed tightly by the research pharmacy using plastic wrap.

Follow up assessment

Subjects met with a research assistant at weeks 2, 4, 6, and 8. Each visit consisted of the assessment of vital signs and side effects. Study medication was dispensed every two weeks. Subjects were asked to return their bottle of medication during each follow up visit; extra quantity of study medication in the bottle was measured to assess adherence. At weeks 4 and 8, psychopathology and cognitive measures were repeated.

Statistical analysis

Statistical analysis was performed using SAS (version 9.2, SAS Institute, Cary, NC). Descriptive statistics were performed to describe demographic and clinical characteristics of the study sample. Group comparisons (insulin versus placebo) for baseline demographic and clinical characteristics were performed using independent t test for continuous variables, and Fisher exact test or Chi-square test for categorical variables. The outcome measures were repeated at different time points (baseline, week 4 and week 8). Therefore, analysis of repeated measures using mixed models was performed to compare the change over time in outcome measures between the two groups while controlling for potential confounding variables. The mixed model approach does not require subjects to have the same number of study visits or measurements, and uses all available data instead of eliminating subjects with missing data, resulting in unbiased estimates of the model parameters when data are missing at random. For all analyses, a p value less than 0.05 (2-tailed) was used for statistical significance.

Results

Sixty-six subjects were screened. Among them, 51 were enrolled and 45 were randomized (21 in the insulin group, 24 in the placebo group). For randomized subjects, 36 were male and 9 female; 34 were Caucasians, 5 African Americans, and 6 in “other” category. The insulin group had a significantly higher education level (12.9 ± 2.3 versus 11.4 ± 2.1 years

respectively, p = 0.026), and also tended to be older (49.2 ± 9.3 versus 43.8 ± 9.2 years old respectively, p=0.057), than the placebo group. There were no significant differences between the two groups in age of illness onset, gender, race, marital status, diagnosis (schizophrenia or schizoaffective disorder), tobacco us, occupation, and the use of antipsychotic agents (data not shown, p's > 0.1).

Psychopathology and cognition outcome measures

Mixed model analysis controlling for age and education showed that intranasal insulin treatment had no significant beneficial effects on the PANSS total score, the scores on the Positive Symptoms, Negative Symptoms, or General Psychopathology subscales, the SANS total score, or the total scores on CDRS and QLS (p's > 0.2). Further, intranasal insulin treatment had no significant beneficial effects on CPT d prime, hits rate, reaction time of hits, false-alarm rate; there were no significant beneficial effects on other cognitive tests (Digit Span, HVLT- immediate recall and delayed recall, verbal fluency, Trails A and B) (p's > 0.2, Table 1).

Side effect assessment

There were no serious adverse events during the study. The side effects reported in more than 5% of the subjects in the insulin group and that occurred at least twice as commonly as in the placebo group were wheezing, coughing, trouble breathing, nasal congestion, hypersalivation, nausea, vomiting, numbness, poor concentration, confusion, insomnia and drowsiness (Table 2). There were no significant differences between the two groups for listed side effects (p's > 0.05). No subject in the insulin group withdrew from the study because of these side effects.

Discussion

We believe that this was the first clinical trial to examine adjunctive repeated dose intranasal insulin therapy in schizophrenia. The 8-week study did not show any beneficial effects of intranasal insulin treatment on psychopathology and cognition in patients with schizophrenia.

Alteration of the phosphoinositide-3-kinase (PI3K)/Akt insulin signaling pathway has been found in schizophrenia. Genetic changes of various components of the PI3K pathway have been reported in patient with schizophrenia[32–34]. Further, available data suggest decreased levels of total and phosphorylated Akt in schizophrenia[35, 36]. Centrally available insulin through intranasal delivery may not be able to overcome impaired insulin signaling in the brains of schizophrenia patients, subsequently failing to potentiate NMDA receptor activity or cause other insulin induced effects on neurotransmission or cell growth that would improve psychopathology.

Previous studies have demonstrated beneficial effects of intranasal insulin treatment, as given here, on cognition in non-schizophrenia populations. More recently, Craft et al. completed a 4-month, double-blind, placebo-controlled trial in patients with mild to moderate Alzheimer disease or amnestic mild cognitive impairment. Subjects received human regular insulin, 20IU (N=36) or 40IU (N=38), or placebo (N=30), twice per day.

They found that both insulin doses had significant beneficial effects in improving cognitive function[37]. The cognitive benefit of intranasal insulin treatment in Alzheimer disease may not generalize to schizophrenia, as the etiology for cognitive deficits in these two disease conditions may not be the same[38].

There are several limitations in the present study. First, despite cognitive benefit of intranasal insulin treatment reported in previous studies, it is uncertain how efficient and consistent insulin delivery through intranasal route actually is and how much insulin reaches the brain. Both experimental factors, such as head position, volume, and method of administration, as well as formulation parameters, such as pH, osmolarity, and inclusion of permeation enhancers or mucoadhesives, can influence drug deposition within the nasal passages and pathways followed into the brain[39]. Other limitations of this study include the relatively small sample size, the relatively short intervention time period (8-week) of the study, the dosing of insulin, the severity of baseline psychopathology and cognitive deficits.

Future research needs to examine and improve the effectiveness of nasal-to-brain insulin delivery, to study long term effects of adjunctive insulin therapy on psychopathology, cognition, and safety in patients with schizophrenia, and to identify biomarkers or subgroups of patients that might predict treatment response.

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Table 1

Psychopathology and cognition outcome measures by treatment groups and the mixed model analysis

	Insulin (N=21)		Placebo (N=24)		Mixed model			
Variable	**Baseline Mean (SD)**	**Week 8 Mean (SD)**	**Baseline Mean (SD)**	**Week 8 Mean (SD)**	**Estimation**	**t Test**	**df**	**p**
PANSS total	77.0 (15.9)	74.3 (19.5)	75.5 (12.7)	74.1 (13.5)	−0.29	−0.73	38	0.47
PANSS Positive	17.1 (4.5)	17.2 (5.6)	17.5 (4.7)	16.8 (5.1)	0.04	0.31	38	0.76
PANSS Negative	20.6 (5.7)	20.8 (6.0)	20.5 (5.3)	20.7 (5.8)	−0.07	−0.52	38	0.61
PANSS General Psychopathology	37.9 (8.8)	36.3 (9.9)	37.5 (7.0)	36.6 (7.4)	−0.25	−1.14	38	0.26
SANS total	29.6 (13.6)	30.8 (15.2)	29.3 (11.8)	33.5 (14.3)	−0.38	−1.22	38	0.23
CDRS total	1.8 (3.1)	2.1 (3.2)	3.2 (4.5)	2.7 (4.4)	0.09	0.86	38	0.40
QLS total	73.4 (16.8)	70.9 (16.3)	71.3 (16.9)	67.0 (16.8)	0.36	1.20	37	0.24
CPT d prime	2.0 (1.0)	1.9 (1.0)	2.1 (0.8)	2.1 (1.0)	−0.02	−1.31	38	0.20
CPT hits rate, %	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	−0.004	−0.96	38	0.35
CPT reaction time of hits, milliseconds	543.6 (121.4)	554.1 (109.4)	528.9 (65.9)	522.9 (73.7)	3.06	0.97	38	0.34
CPT false-alarm rate, %	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	−0.001	−0.24	38	0.82
Digit Span total	12.7 (3.6)	13.3 (4.0)	14.0 (5.1)	14.1 (4.9)	0.08	0.79	38	0.43
HVLT immediate recall total	18.2 (6.6)	21.4 (8.4)	19.9 (6.5)	23.6 (7.1)	−0.03	−0.14	38	0.89
HVLT delayed recall	5.7 (3.6)	6.8 (3.6)	5.9 (3.3)	7.8 (3.2)	−0.01	−0.15	38	0.88
Verbal fluency total	29.7 (12.0)	27.9 (11.6)	26.0 (13.8)	28.0 (13.3)	−0.37	−1.38	38	0.17
Trails A, seconds	55.1 (28.4)	60.6 (35.0)	55.3 (24.6)	52.3 (23.2)	0.85	1.13	38	0.26
Trails B, seconds	131.0 (69.0)	131.5 (62.0)	126.2 (52.4)	118.6 (44.1)	2.14	0.99	28	0.33

Notes: 1) Analysis of repeated measures using mixed models was performed to compare the change over time in outcome measures between the two groups while controlling for age and education; 2) PANSS, the Positive and Negative Syndrome Scale; 3) SANS, the Scale for Assessment of Negative Symptoms; 4) CDRS, the Calgary Depression Rating Scale; 5) QLS, the Heinrichs-Carpenter Quality of Life Scale; 6) CPT, the Continuous Performance Test; 7) HVLT, the Hopkins Verbal Learning Test.

Table 2

Side effect assessment*

	Insulin (N=21)		Placebo (N=24)		p value
Adverse event	**N**	**%**	**N**	**%**	
Wheezing	2	10	0	0	0.41
Coughing	2	10	0	0	0.41
Trouble breathing	1	5	0	0	1.00
Nasal congestion	2	10	1	4	0.92
Hypersalivation	1	5	0	0	1.00
Nausea	1	5	0	0	1.00
Vomiting	1	5	0	0	1.00
Numbness	1	5	0	0	1.00
Poor concentration	2	10	1	4	0.92
Confusion	1	5	0	0	1.00
Insomnia	4	19	0	0	0.09
Drowsiness	2	10	0	0	0.92

* occurred in more than 5% of the subjects taking insulin and was at least twice as common as in the placebo group.