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No effect of adjunctive, repeated dose intranasal insulin treatment on body metabolism in patients with schizophrenia

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Abstract

Objective—This study examined the effect of adjunctive intranasal insulin therapy on body metabolism in patients with schizophrenia.

Method—Each subject had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and had been on stable dose of antipsychotic agent for at least one month. In an 8-week randomized, double-blind, placebo-controlled study, subjects received either intranasal insulin (40IU 4 times per day) or placebo. The whole body dual-energy X-ray absorptiometry (DXA) was used to assess

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body composition. Lipid particles were assessed using nuclear magnetic resonance (NMR) spectroscopy. All assessments were conducted at baseline, and repeated at week 8.

Results—A total number of 39 subjects completed the study (18 in the insulin group, 21 in the placebo group). There were no significant differences between the two groups in week 8 changes for body weight, body mass index, waist circumference, as well as various measures of lipid particles (p′s > 0.100). The DXA assessment showed no significant differences between the two groups in week 8 changes for fat mass, lean mass or total mass (p's > 0.100).

Conclusion—In the present study, adjunctive therapy of intranasal insulin did not seem to improve body metabolism in patients with schizophrenia. The implications for future studies were discussed.

Keywords

intranasal insulin; schizophrenia; body composition; lipids

1. Introduction

Patients with schizophrenia have a 20% shorter life expectancy than the general population, and a greater vulnerability to some serious medical illnesses (Marder et al. 2004). The prevalence of obesity among individuals with schizophrenia and affective disorders is 1.5 – 2.0 times higher than in the general population (Karpati et al. 2004). While atypical antipsychotic agents have many notable benefits compared to conventional antipsychotic agents in treating schizophrenia and other psychiatric illnesses, their use has been associated with reports of weight gain and obesity, which are associated with increased risk of other metabolic complications including dyslipidemia, diabetes, and cardiovascular diseases (Henderson 2005).

The maintenance of weight is the result of a balance between energy intake and expenditure (Rosenbaum et al. 1997). Resting energy expenditure (REE) is variable among individuals and is the largest component of energy expenditure, comprising 60-80% of non-activity total energy expenditure (Goran 2000). In recent years, insulin also emerged as an important determinant of energy expenditure (Perseghin et al. 2002; Schwartz et al. 1995). A recent study from our group demonstrated that higher fasting serum insulin levels are associated with increased REE in non-diabetic schizophrenia patients (Fan et al. 2006). The mechanisms linking insulin and REE are still unclear. However, this linkage could be at least partially due to the interaction between insulin and the increased activity of the sympathetic nervous system, which is consequently associated with increased REE (Berne et al. 1992; Vollenweider et al. 1993).

One important action of insulin in the brain is on food intake and weight control (Schwartz and Porte 2005). Centrally available insulin reduces food intake and body weight in a dose-dependent manner when chronically infused into the ventricular system in rats (Brief and Davis 1984). These effects are also obtained in rats after a single acute injection of insulin (Air et al. 2002). On the other hand, administering insulin antibodies into ventromedial areas of hypothalamus increases food intake and body weight (Gerozissis 2003), and the deletion of central insulin receptors is accompanied by hyperphagia, obesity and hyperlipidemia in rats (Bruning et al. 2000; Obici et al. 2002).

Previous studies examined the effect of centrally available insulin through intranasal delivery on food intake and body composition in healthy subjects. A study of 8-week intranasal insulin treatment (40IU 4 times per day) in 12 healthy men and 8 healthy women was reported (Hallschmid et al. 2004). Insulin treated men lost 1.28 kg body weight and 1.38

kg body fat, and their waist circumference decreased by 1.63 cm ($p's < 0.05$); in contrast, insulin treated women did not lose body fat but gained 1.04 kg body weight ($p < 0.05$). In a separate study, single dose of 160 IU insulin or placebo were administered intranasally to a total of 32 healthy subjects (14 men, 18 women), and then food intake from an ad libitum breakfast buffet was measured. Insulin treatment decreased food intake in men but not in women (Benedict et al. 2008). These findings suggest a gender difference of insulin signaling in the brain, which is consistent with the results from animal studies (Clegg et al. 2003).

Intranasal administration of insulin, which is non-invasive and does not induce hypoglycemic reaction (Hilsted et al. 1995), provides a practical tool to examine the potential role of insulin in improving metabolic disturbances in patients with schizophrenia.

We conducted an 8-week, randomized, placebo-controlled, double-blinded study to examine how adjunctive insulin therapy might affect psychopathology, cognition and body metabolism in patients with schizophrenia. The findings on psychopathology and cognition, as well as the tolerability of study drug, have been reported elsewhere (Fan et al., in press). The study failed to demonstrate any significant benefit of intranasal insulin treatment in improving clinical symptoms of schizophrenia or cognitive function even though intranasal insulin was well tolerated by the study subjects. We now present the findings on body composition and lipid particle sizes using whole body dual-energy X-ray absorptiometry (DXA) and nuclear magnetic resonance (NMR) spectroscopy respectively.

2. Method

2.1. 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). 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. Exclusion criteria were: 1) inability to provide informed consent; 2) current substance abuse; 3) significant medical conditions including liver or renal dysfunction, pulmonary disease, or unstable cardiovascular disease; 4) diagnosis of diabetes mellitus; 5) being pregnant or lactating (female). The study was approved by the institutional review boards of the Massachusetts General Hospital (MGH) and the Massachusetts Department of Mental Health.

2.2. Procedure

At baseline, eligible subjects completed an assessment which included the Positive and Negative Syndrome Scale (PANSS) and other rating scales, a cognitive battery, and treatment emergent side effects (Fan et al., in press). Each subject then underwent the following baseline measures at the MGH Clinical Research Center (CRC): nutrition assessment including anthropometric measures, indirect calorimetry, dual Energy X-ray Absorptiometry (DXA), fasting blood samples for laboratory assays.

After baseline measures at the MGH CRC 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 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 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 used in this study was similar to the devices used to administer intranasal insulin in published studies. 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.

2.3. Nutritional assessment

The methods for height, weight, circumferences, and indirect calorimetric measures, resting energy expenditure (REE) and waist-hip ratio calculations are described in detail elsewhere (Henderson 2005). Body mass index (BMI) was calculated based on weight and height (weight (kg) / [height (m)]^2). Body composition was determined using the DXA (Hologic QDR-4500; Hologic Inc, Waltham, MA). DXA has been validated for body composition measurement (Glickman et al. 2004). Body composition data were presented as bone mineral content (BMC, in grams), fat mass (in grams), lean mass (in grams), and total body mass (BMC + fat mass + lean mass, in grams); in addition, fat percentage was calculated as fat mass (in grams) divided by total mass (in grams). Data were presented separately for trunk, abdomen and total body.

2.4. Laboratory Assays

Laboratory assays were performed by the Chemistry Lab and the CRC Core Lab of the MGH. Insulin immunometric assays were performed using an Immulite Analyzer (Diagnostic Product Corporation, Los Angeles, CA) with an intra-assay coefficient of variation of 4.2-7.6%. Fasting plasma glucose was measured with a hexokinase reagent kit (A-gent glucose test, Abbott, South Pasadena, CA). Glucose assays were run in duplicate, and the intra-assay coefficient of variation ranged from 2% to 3%. The homeostasis model of assessment of insulin resistance (HOMA-IR) was calculated by the following formula: [fasting serum insulin concentration (μIU/mL) X fasting plasma glucose concentration(mmol/L)/22.5 (Hermans et al. 1999). Hemoglobin A1C (HbA1c) was measured with high performance liquid chromatography using an automated analyzer (normal range 4.5–6.5%) (SmithKline, Van Nuys, CA). Fasting total plasma cholesterol and triglyceride levels were measured enzymatically (McNamara and Schaefer 1987), and the HDL cholesterol fraction was measured after precipitation of low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) with dextran sulfate-magnesium (Warnick et al 1982). LDL levels were determined by the direct LDL reagents (Roche Diagnostics, Indianapolis, IN). Serum levels of C- reactive protein (CRP) were measured via a high-sensitivity latex-enhanced immunonephelometric assay on a BN II analyzer (Dade Behring, Newark, Del). Lipoprotein subclass concentrations and the LDL particle size were determined using the NMR spectroscopy (LipoScience, Raleigh, NC) (Otvos 2002; Otvos et al. 1992). NMR capitalizes on the fact that each lipoprotein subclass particle of a given size emits its own characteristic signal. Conversion factors relating signal amplitudes to subclass concentrations expressed in particle concentration units are then applied. In the present study, the following lipoprotein subclasses were assessed: LDL particle, small LDL particle, large HDL particle, and large VLDL particle.

2.5. Follow up assessment

Subjects met with a research assistant at weeks 2, 4, 6. Study visits consisted of assessment of vital signs and side effects. Subjects were required to bring in the nasal spray device during each study visit. The plastic seal was checked, and the residual volume of insulin in the container was measured and recorded. A new device filled with either insulin or placebo was dispensed during each study visit. At week 8, all baseline assessments were repeated, including rating scales, side effects, anthropometric measures and laboratory assays.

2.6. Statistical analysis

Statistical analysis was performed using SPSS (version 19.0, SPSS Inc., Chicago). Descriptive statistics were performed to describe demographic and clinical characteristics of the study sample. Group comparisons were performed using the independent t test for continuous variables, and the Fisher exact test or Chi-square test for categorical variables. Analysis of covariance (ANCOVA) was used to compare change scores from baseline to week 8 between the two treatment groups controlling for baseline scores and potential confounding variables. For all analyses, a p value less than 0.05 (2-tailed) was used for statistical significance.

3. Results

Forty-five subjects were randomized (21 in the insulin group, 24 in the placebo group); 39 subjects completed the week-8 metabolic assessment, therefore were included in the final data analysis. The insulin group (N=18) tended to have a higher education level ($p = 0.060$), and also tended to be older ($p=0.086$) than the placebo group (N=21). There were no significant differences between the two groups in age of illness onset, BMI, HOMA-IR, gender, race, marital status, diagnosis (schizophrenia or schizoaffective disorder), tobacco us, occupation, and the use of antipsychotic agents (p's > 0.1, Table 1).

3.1 Anthropometric measures

After controlling for baseline values, age and education, the ANCOVA analysis showed no significant differences between the two groups in week 8 changes for body weight, BMI, waist circumference, waist-hip ratio, or resting energy expenditure (p′s > 0.100). The DXA assessment showed no significant differences between the two groups in week 8 changes for BMC, fat mass, fat percentage, lean mass or total mass - in trunk, abdomen, or total body (p′s > 0.100) (Table 2).

3.2. Laboratory measures

The ANCOVA analysis controlling for baseline values, age and education showed that there were no significant differences between the two groups in week 8 changes for fasting glucose and insulin, HOMA-IR, HbA1c, CRP, total cholesterol, LDL, HDL, triglycerides, LDL particle size, LDL particle number concentration, small LDL particle number concentration, large HDL particle number concentration, and large VLDL particle number concentration (p′s > 0.100) (Table 3).

3.3. Subgroup analysis by gender or olanzapine treatment status

Data analysis was repeated within each gender subgroup, or within subgroups based on olanzapine treatment status. In each subgroup, the results were similar as in the entire study sample - no significant differences were found between the insulin group and the placebo group in week 8 changes for various metabolic measures (data not shown).

4. Discussion

This was the first study to examine the potential impact of adjunctive intranasal insulin treatment on body metabolism in patients with schizophrenia using relatively sophisticated techniques including DXA to assess body composition, and NMR spectroscopy to measure lipid particle size. The 8-week study failed to show beneficial effect of intranasal insulin treatment on any of the major metabolic outcome measures.

Previous studies in healthy human subjects have suggested a gender difference in insulin signaling in the brain; intranasal insulin treatment decreased food intake, body weight and fat in males but not in females (Benedict et al. 2008; Hallschmid et al. 2004). However, in our study, intranasal insulin therapy did not seem to show benefit on body metabolism in either gender subgroup.

Studies have suggested that antipsychotic medications may have direct impact on appetite and food intake. For example, significant increases in food intake and weight gain were reported in healthy males after 15 days of olanzapine administration; these increases were independent of changes in energy expenditure or insulin sensitivity (Fountaine et al. 2010) . Further, increases in hunger coupled with decreases in satiety have been reported consistently following olanzapine administration (Case et al. 2010). It is possible that the anorexigenic effect of intranasal insulin administration was not able to mitigate the orexigenic effect of antipsychotic treatment that the patients received in the present study. In the present study, olanzapine treatment status did not seem to affect the negative findings on metabolic measures.

In the arcuate nucleus of the hypothalamus, a highly integrated neuropeptidergic network constitutes the down-stream signaling cascades responsible for a balanced regulation of anabolic and catabolic pathways. Anabolic pathways trigger food intake and decrease energy expenditure – leading to weight gain; while catabolic pathways decrease food intake and increase energy expenditure and consequently lead to weight loss (Schwartz et al. 2003). Neurons synthesizing α-melanocyte-stimulating hormone (α-MSH), a melanocortin derived from pre-proopiomelanocortin (POMC), are essential for catabolic signal transduction (Fan et al. 1997). Insulin increases POMC gene expression (Brown et al. 2006). It is assumed that the ability of insulin to reduce food intake relies on the stimulation of POMC arcuate neurons, resulting in the release of α-MSH (Benoit et al. 2002). Alteration of the insulin signaling pathway has been found in schizophrenia (Duan et al. 2005; Saito et al. 2005; Stopkova et al. 2004) (Thiselton et al. 2008; Zhao et al. 2006). Centrally available insulin through intranasal delivery may not be able to overcome impaired insulin signaling in the brains of schizophrenia patients, subsequently failing to affect catabolic or anabolic signal transduction in the hypothalamus.

The negative findings in this study might be explained by other factors. One major challenge in intranasal drug delivery is the uncertainty of how efficient the drug is actually delivered to the brain. A previous study in healthy young adults demonstrated that a single dose of 40 IU regular human insulin through intranasal administration resulted in increased insulin levels in the cerebrospinal fluid (CSF) within 10 minutes with peak levels reached within 30 minutes (Born et al. 2002). It is unclear weather intranasal insulin delivery in the present study achieved similar pharmacokinetic effectiveness in the CSF and brain. The relatively short intervention time period (8-week), the small sample size, and the significant metabolic abnormalities at baseline in at least some of the study subjects might be other important considerations to explain the negative findings.

Future research needs to study longer term effect of adjunctive insulin therapy on metabolism in patients with schizophrenia, and to identify biomarkers, that might predict

treatment response. Potential biomarkers include metabolic changes in the brain as detected by single photon emission computed tomography (SPECT) and positron-emission tomography (PET), or inflammation and oxidative stress that are related to brain insulin signaling and resistance (de la Monte).

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Table 1

Baseline demographic and clinical characteristics of the study sample

Variable	Insulin (N=18)		Placebo (N=21)		*p*
	Mean	SD	Mean	SD	
Age (years)	48.7	9.7	43.3	9.6	0.086
Education (years)	12.7	2.1	11.4	2.0	0.060
Age of illness onset (years)	30.1	10.7	24.1	11.4	0.139
BMI (kg/m^2)	28.5	6.2	32.2	5.6	0.100
HOMA-IR	1.82	1.18	3.36	3.17	0.067
	N	%	N	%	
Gender					0.418
Male	16	89	16	26	
Female	2	11	5	24	
Race					0.560
Caucasian	14	78	14	67	
African American	2	11	3	14	
Other	2	11	4	19	
Marital status					0.589
Single	15	83	16	76	
Married	1	6	0	0	
Separated	1	6	1	5	
Divorced	1	6	3	14	
Widowed	0	0	1	5	
Diagnosis					0.748
Schizophrenia	12	67	15	71	
Schizoaffective disorder	6	33	6	29	
Tobacco use					0.455
Yes	9	50	8	38	
No	9	50	13	62	
Occupation					0.178
Unemployed	10	56	15	71	

Variable	Insulin (N=18)		Placebo (N=21)		*p*
Employed	2	11	4	19	
Unknown	6	33	2	10	
Antipsychotic agent					0.835
Olanzapine	10	56	11	52	
Others	8	44	10	48	

Note: 1) The total percentages may not equal to 100% because of rounding; 2) BMI, body mass index; 3) HOMA-IR, homeostasis model of assessment of insulin resistance.

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Table 2

Changes in anthropometric assessment over 8-week study period

	Insulin (N=18)				Placebo (N=21)				*p*
	Baseline		Week 8 change		Baseline		Week 8 change		
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Body weight (kg)	82.5	16.2	0.8	1.9	95.8	16.8	-2.8	9.6	0.411
BMI (kg/m^2)	28.5	6.2	0.3	0.6	32.2	5.6	-0.1	0.9	0.167
Waist circumference (umbilicus, cm)	101.7	11.3	1.2	3.1	111.9	15.4	0.04	2.3	0.212
Waist-hip ratio	0.99	0.06	0.01	0.03	1.00	0.08	-0.002	0.04	0.375
Resting energy expenditure (kcal/day)	1 772	371	65	284	1 967	429	-72	372	0.627
DXA BMC (g)									
Trunk	571	92	4	29	637	106	-4	29	0.379
Abdomen	66	31	-3	19	62	11	0.2	8	0.529
Total body	2 342	345	-5	48	2 442	286	4	61	0.612
DXA fat mass (g)									
Trunk	11 846	5 312	288	894	16 430	6 807	14.8	989	0.852
Abdomen	3 378	1 648	35.7	305	4 753	2 253	9	434	0.679
Total body	23 393	11 154	315	1 193	29 404	12 036	1 011	4 781	0.207
DXA fat percentage (%)									
Trunk	27.8	8.9	0.4	1.5	33.0	8.9	0.1	1.2	0.935
Abdomen	29.1	10.1	0.7	1.3	34.7	8.9	-0.03	1.8	0.540
Total body	27.3	9.1	0.2	0.9	31.5	7.3	-0.01	0.9	0.813
DXA lean mass (g)									
Trunk	28 485	4 025	125	846	30 822	4 576	-80	822	0.665
Abdomen	7 596	1 255	-149	617	8 178	1 730	63	488	0.293
Total body	57 880	8 629	479	1 652	61 849	9 827	-41	1 455	0.145
DXA total mass (g)									
Trunk	42 569	11 677	-1 249	6 951	47 889	9 955	-70	1 402	0.586
Abdomen	11 037	2 442	-113	966	12 993	3 764	72	717	0.316
Total body	84 216	16 524	789	2 318	93 469	18 658	1 202	6 654	0.270

Notes: 1) Week 8 change equals week 8 value minus baseline value; 2) BMI, body mass index; 3) MAQ, Modifiable Activity Questionnaire (average hours of activity per week; 4) DXA, dual-energy X-ray absorptiometry; 5) BMC, bone mineral content; 6) p values were based on ANCOVA comparing between group differences in week 8 changes controlling for baseline values, age and education.

Table 3

Changes in glucose metabolism, lipids and other metabolic parameters over 8-week study period

	Insulin (N=18)				Placebo (N=21)				*p*
	Baseline		Week 8 change		Baseline		Week 8 change		
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Fasting plasma glucose (mg/dL)	81.2	17	4.8	16	88	13	-3	14	0.375
Fasting serum insulin (μ IU/mL)	8.7	4.9	0.4	2.6	14.7	12,6	0.6	7.5	0.686
HOMA-IR	1.82	1.18	0.15	0.58	3.36	3.17	-0.04	1.93	0.935
HbA1c (%)	5.6	0.6	0.03	0.2	5.7	0.5	-0.13	0.4	0.310
C-reactive protein (mg/L)	3.7	3.9	1.64	3.86	3.8	2.9	0.38	1.51	0.436
Total cholesterol (mg/dL)	185	49	-1	39	187	35	0	21	0.948
Direct LDL (mg/dL)	117	41	-5	26	122	30	-0.06	23	0.488
HDL (mg/dL)	43	9	1	8	41	6	-1	4	0.595
Triglycerides (mg/dL)	144	52	-8	67	140	90	-0.5	43	0.630
LDL particle number (nmol/L)	1 414	434	16	263	1 508	365	26	333	0.504
LDL particle size (nm)	21.0	0.5	-0.1	0.8	20.7	0.7	0.03	0.4	0.617
Small LDL particle number (nmol/L)	836	387	45	370	924	413	53	326	0.436
Large HDL particle number (μmol/L)	6.3	3.5	0.29	1.8	4.9	3.2	0.22	1.79	0.864
Large VLDL particle number (nmol/L)	4.3	4.1	-1.2	4.1	4.6	6.7	-0.62	2.3	0.650

Notes: 1) Week 8 change equals week 8 value minus baseline value; 2) HOMA-IR, homeostasis model of assessment of insulin resistance; 3) HbA1c, hemoglobin A1c; 4) p values were based on ANCOVA comparing between group differences in week 8 changes controlling for baseline values, age and education.