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Atypical antipsychotic medications increase postprandial triglyceride and glucose levels in male rats: Relationship with stearoyl-CoA desaturase activity

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ABSTRACT

Recent preclinical and clinical evidence suggests that the stearoyl-CoA desaturase-1 (*Scd1*) enzyme plays a key role in the regulation of triglyceride (TG) biosynthesis and insulin sensitivity, and *in vitro* studies have found that antipsychotic medications up-regulate *Scd1* mRNA expression. To investigate these effects *in vivo*, rats were treated with risperidone (1.5, 3, and 6 mg/kg/d), paliperidone (1.5, 3, and 6 mg/kg/d), olanzapine (2.5, 5, and 10 mg/kg/d), quetiapine (5, 10, and 20 mg/kg/d), haloperidol (1, and 3 mg/kg/d) or vehicle through their drinking water for 40 days. Effects on liver *Scd1* mRNA expression and an index of *Scd1* activity (the plasma 18:1/18:0 ratio, 'desaturation index') were determined, as were postprandial plasma triglyceride (TG), glucose, insulin, and polyunsaturated fatty acid (PUFA) levels. All atypical antipsychotics increased the plasma 18:1/18:0 ratio, but not liver *Scd1* mRNA expression, at doses found to also increase plasma TG levels. Among all rats (n = 122), the plasma 18:1/18:0 ratio accounted for 56% of the variance in TG concentrations. The plasma 18:1/18:0 ratio was also positively associated with erythrocyte and heart membrane phospholipid 18:1*n*-9 composition. All antipsychotics except risperidone increased glucose levels at specific doses, and none of the antipsychotics significantly altered insulin levels. The plasma 18:1/18:0 ratio accounted for 20% of the variance in glucose levels. Plasma omega-3 and omega-6 PUFA levels were inversely correlated with the plasma 18:1/18:0 ratio and TG and glucose levels. These *in vivo* data demonstrate that different atypical antipsychotic medications increase the plasma 18:1/18:0 ratio in association with elevations in postprandial TG and glucose levels, and that concomitant elevations in PUFA biosynthesis oppose these effects.

1. Introduction

Treatment-emergent hyperlipidemia, clinically significant weight gain, and insulin resistance are frequently observed in schizophrenic patients following chronic exposure to some atypical antipsychotic medications, and may increase risk for coronary heart disease and type 2 diabetes (Henderson, 2007; Meyer, 2001; Newcomer, 2007). The severity of hyperlipidemia and insulin resistance have been found to be greater following treatment with the atypical antipsychotics olanzapine and quetiapine compared with risperidone and typical antipsychotics (Garman et al., 2007; Meyer and Koro, 2004; Newcomer et al., 2002). Moreover, postprandial (non-fasting) triglyceride (TG) levels, which are a stronger predictor of cardiovascular risk (Eberly et al., 2003; Langsted et al., 2008; Bansal et al., 2007), are greater following treatment with olanzapine and quetiapine compared with risperidone and typical antipsychotics (Meyer et al., 2008; Smith et al., 2010). Furthermore, greater increases in glucose levels in response to an oral glucose bolus are observed in patients treated with olanzapine compared with risperidone (Smith et al., 2009). Despite this body of clinical evidence, however, the mechanisms mediating antipsychotic-induced elevations in TG synthesis and insulin resistance remain poorly understood.

Emerging evidence from rodent and clinical studies suggests that stearoyl-CoA desaturase-1 (SCD1, Δ9-desaturase) plays a central role in regulating TG biosynthesis and insulin sensitivity. SCD1 mediates oleic acid (18:1*n*-9) synthesis from stearic acid (18:0), and 18:1 is a substrate required for the *de novo* synthesis of phospholipids, cholesteryl esters, and TG (Paton and Ntambi, 2009). Mouse studies have demonstrated that *Scd1* mutation is associated with reductions in Scd1 activity (liver and plasma 18:1/18:0 ratios) and deficits in TG biosynthesis (Attie et al., 2002; Miyazaki et al., 2000, 2001). Consistent with TG being stored in adipose tissue, *Scd1* mutant mice also exhibit reduced adiposity independent of body weight gain, and

Abbreviations: Scd1, stearoyl-CoA desaturase-1; 18:0, stearic acid; 18:1, oleic acid; PUFA, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid.

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are resistance to diet-induced obesity (Ntambi et al., 2002). *Scd1* mutant mice also exhibit increased insulin sensitivity (Rahman et al., 2003). Similarly, pharmacological inhibition of the Scd1 enzyme reduces elevated TG and glucose levels in rodent disease models (Issandou et al., 2009; Uto et al., 2010). In human subjects, elevations in the plasma 18:1/18:0 ratio ('desaturation index'), a putative index of SCD1 enzyme activity, is positively correlated with plasma TG levels and insulin resistance (Attie et al., 2002; Flowers and Ntambi, 2009; Mar-Heyming et al., 2008; Paillard et al., 2008; Warensjö et al., 2007). This body of evidence suggests that SCD1 expression and activity are required for TG biosynthesis and regulate insulin sensitivity.

A number of *in vitro* studies have found that different antipsychotic medications up-regulate the expression of lipogenic genes regulated by the sterol regulatory element-binding protein (SREBP) including *SCD1* (Hulver et al., 2005; Lauressergues et al., 2010; Polymeropoulos et al., 2009; Raeder et al., 2006). Moreover, schizophrenic patients treated with olanzapine exhibit greater *SCD1* mRNA expression in peripheral blood cells compared with drug-free patients (Vik-Mo et al., 2008). However, SCD1 mRNA expression and activity are regulated by a myriad of dietary and hormonal factors not accounted for in prior studies, including glucose, polyunsaturated fatty acids (PUFA), insulin, and leptin. For example, both omega-3 and omega-6 PUFAs repress *Scd1* expression at the level of transcription and mRNA stability (Landschulz et al., 1994; Ntambi, 1999; Sessler et al., 1996). Omega-3 PUFAs also reduce elevated TG levels in rodent disease models (Hassanali et al., 2010; Lu et al., 2011; Mustad et al., 2006) and in schizophrenic patients treated with atypical antipsychotic medications (Caniato et al., 2006; Peet et al., 2002). In previous studies we found that chronic treatment with different antipsychotic medications up-regulate PUFA biosynthesis in rats (McNamara et al., 2009a, 2011). Together, these findings suggest that antipsychotic effects on Scd1 expression and activity are modulated by PUFAs, and emphasize the importance of controlling for dietary PUFA intake.

The primary objective of the present study was to determine the effects of chronic exposure to different antipsychotic medications on liver *Scd1* mRNA expression and activity *in vivo*, and to determine associations with postprandial TG, glucose, insulin and PUFA levels. Based on the evidence reviewed above, our specific prediction was that chronic exposure to atypical antipsychotic medications would up-regulate hepatic *Scd1* mRNA expression and activity, and that these effects would be positively correlated with postprandial TG levels and inversely correlated with omega-3 PUFA levels.

2. Materials and methods

2.1. Animals and diet

Adult (P56) male Long-Evans hooded rats were purchased from Harlan-Farms Indianapolis, IN. Upon arrival, all rats were maintained on the same custom research diet (TD.04285, Harlan-TEKLAD, Madison, WI). This diet contained casein (vitamin-free) 200 g/kg, L-cystine 3 g/kg, sucrose 270 g/kg, dextrose monohydrate 99.5 g/kg, corn starch 200 g/kg, maltodextrin 60 g/kg, cellulose 50 g/kg, mineral mixture AIMN-93 G-MX 35 g/kg, vitamin mixture AIN-93-VX 10 g/kg, choline bitartrate 2.5 g/kg, and TBHQ (antioxidant) 0.02 g/kg. The diet contained 18:0 (9.4% of total fatty acids) and 18:1*n*-9 (6.7% of total fatty acids). For complete diet lipid composition see Table 1 in McNamara et al. (2008). Rats were housed 2 per cage, and food and fluids were available *ad libitum*. Paired housing was selected to avoid confounding effects of single-housing stress on primary outcome measures (Pérez et al., 1997). Rats were maintained under standard vivarium conditions on a 12:12 h light:dark cycle. Food (g/kg/d) and fluid (ml/kg/d) intake and body weight were routinely recorded. Rats were sacrificed by decapitation on P99-101 in a counter-balanced manner relative to the removal of food hoppers at 9:00 am. Trunk blood was collected into EDTA-coated tubes, plasma isolated by centrifugation, and erythrocytes washed 3× with 4 °C 0.9% NaCl. Heart and liver samples were also collected. All samples were stored at −80 °C deg. All experimental procedures were approved by the University of Institutional Animal Care and Use Committee, and adhere to the guidelines set by the National Institutes of Health.

2.2. Drug administration

On P60, rats (n = 122) were randomly assigned to receive drug vehicle (0.1 M acetic acid diluted in deionized water), risperidone (1.5, 3, and 6 mg/kg/d; supplied by Ortho-McNeil Janssen Scientific Affairs LLC), paliperidone (1.5, 3, and 6 mg/kg/d, supplied by Ortho-McNeil Janssen Scientific Affairs LLC), olanzapine (2.5, 5, and 10 mg/kg/d, supplied by Eli Lilly and Company), quetiapine (5, 10, and 20 mg/kg/d, supplied by AstraZeneca Pharmaceuticals), or haloperidol (1 and 3 mg/kg/d, Sigma-Aldrich Chemicals) through their drinking water (n = 8/drug dose). Doses of risperidone, olanzapine, and haloperidol were selected based on prior studies finding production of therapeutically-relevant plasma concentrations in rats following chronic oral administration (Andersson et al., 2002; McNamara et al., 2009a; Terry et al., 2005). Doses of quetiapine were selected based on prior behavioral and neurochemical studies finding significant effects within this dose range (Migler et al., 1993; Tarazi et al., 2002), and to avoid sedative effects observed at higher doses (≥40 mg/kg, Betz et al., 2005). Drugs were administered through the rat's drinking water to avoid daily injection stress and surgical implantation of mini-pumps, to mimic oral administration in human patients, and to permit maintenance of drug dose in accordance with age-related increases in body weight and fluid intake. For three days prior to drug delivery, 24 h water consumption was determined for each cage using bottle weights (1 g water = 1 ml water), and ml water intake/mean kg body weight calculated. All drugs were dissolved and diluted in 0.1 M acetic acid to prepare a stock solution (stored at 4 deg) which was added to tap water at a volume required to deliver the targeted daily dose. To maintain intake of the targeted daily dose, drug concentrations were adjusted to mean daily fluid intake and mean body weight (ml/kg/d) every 3 days. Red opaque drinking bottles were used to protect drug from light degradation. Rats were maintained on their respective drug and dose until being sacrificed on P99-101 (39–41 days of treatment). Dehydration was routinely monitored over the course of the study using the skin tenting method.

2.3. Fatty acid composition

The gas chromatography procedure used to determine plasma, erythrocyte, and heart fatty acid composition has been described in detail previously (McNamara et al., 2009a). Briefly, total fatty acid composition was determined with a Shimadzu GC-2014 (Shimadzu Scientific Instruments Inc., Columbia MD). Analysis of fatty acid methyl esters was based on area under the curve calculated with Shimadzu Class VP 4.3 software. Fatty acid identification was based on retention times of authenticated fatty acid methyl ester standards (Matreya LLC Inc., Pleasant Gap PA). Data are expressed as weight percent of total fatty acids (mg fatty acid/100 mg fatty acids). All analyses were performed by a technician blinded to treatment. We focused our primary analysis on the principle substrate and product of Scd1, stearic acid (18:0) and oleic acid (18:1*n*-9), respectively. The plasma 18:1/18:0 ratio ('desaturation index') was calculated as an index of liver *Scd1* activity (Attie et al., 2002). Principle plasma PUFAs, including eicosapentaenoic acid (EPA, 20:5*n*-3), docosahexaenoic acid (DHA, 22:6*n*-3), linoleic acid (18:2*n*-6), and arachidonic acid (20:4*n*-6), were also investigated.