OBJECTIVE—Olanzapine (OLZ) is an atypical antipsychotic whose clinical efficacy is hampered by side effects including weight gain and diabetes. Recent evidence shows that OLZ alters insulin sensitivity independent of changes in body weight and composition. The present study addresses whether OLZ-induced insulin resistance is driven by its central actions.

RESEARCH DESIGN AND METHODS—Sprague-Dawley rats received an intravenous (OLZ-IV group) or intracerebroventricular (OLZ-ICV group) infusion of OLZ or vehicle. Glucose kinetics were assessed before (basal period) and during euglycemic-hyperinsulinemic clamp studies.

RESULTS—OLZ-IV caused a transient increase in glycemia and a higher rate of glucose appearance (EGP) compared with vehicle-IV. Consistent with an elevation in EGP, the OLZ-IV group had higher hepatic mRNA levels for the enzymes glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. Phosphorylation of hypothalamic AMP-activated protein kinase (AMPK) was increased in OLZ-IV rats compared with controls. Similarly, an intracerebroventricular infusion of OLZ resulted in a transient increase in glycemia as well as a higher Rg in the basal period. During the hyperinsulinemic period, OLZ-ICV caused a decreased GIR, an increased EGP, but no change in hepatic glycogen synthesis and, more specifically, the regulation of hepatic insulin resistance.

CONCLUSIONS—Acute central nervous system exposure to OLZ induces hypothalamic AMPK and hepatic insulin resistance, pointing to a hypothalamic site of action for the metabolic dysregulation of atypical antipsychotics. Diabetes 59:2418–2425, 2010

A typical antipsychotics, such as olanzapine (OLZ), account for the majority of antipsychotic drugs prescribed for the treatment of schizophrenia and bipolar disorders. Furthermore, a multicenter double-blind comparison between several antipsychotics has underscored the efficacy of OLZ compared with other earlier-generation antipsychotics (1). However, atypical antipsychotics, in particular OLZ, have been associated with serious metabolic side effects, including weight gain, dyslipidemia, and diabetes (2,3).

Although it is established that atypical antipsychotics, especially OLZ, are strongly associated with increased weight gain in humans, little is known regarding the mechanisms responsible for this effect (4). Acutely, two atypical antipsychotics, clozapine and OLZ, increase the consumption of a high-calorie fat emulsion in rodents (5). Further, weight gain in rats treated for 7 days with OLZ was accounted for by increased food intake (6). However, hyperphagia and weight gain are not universally observed in animal models of antipsychotic treatment, but increased body adiposity is strongly associated with chronic OLZ administration (7,8).

In general, body adiposity positively correlates with insulin resistance. Indeed, short-term (4 weeks) treatment with OLZ caused increased visceral adiposity, which was associated to markedly reduced hepatic insulin sensitivity (9,10), a common feature of obesity and type 2 diabetes. However, recent evidence (11–13) suggests that OLZ can acutely impair insulin sensitivity, in the absence of changes in adiposity. OLZ, as well as other atypical antipsychotics, acts as an antagonist for many neurotransmitter receptors, including dopamine, serotonin, histamine, and acetylcholine (14,15). To date, the identity and location of the receptors blocked by OLZ that are implicated in the disruption of glucose metabolism remain unknown. The hypothalamus has long been implicated in the regulation of energy balance as well as glucose homeostasis. Circulating hormones and nutrients are acting in the hypothalamus, and specifically the arcuate nucleus (ARC), to modulate glucose metabolism (16). One likely site of action for the deleterious effects of OLZ on glucose homeostasis is in the ARC, since several receptors for which OLZ has moderate to high affinity are expressed in this hypothalamic area. Both serotonin and dopamine can inhibit firing in ARC neurons (17), whereas D2 receptor agonists reduce and antagonists increase the expression of ARC neuropeptide-Y (NPY) (18). In addition, serotonergic inputs in ARC are shown to regulate NPY/AgRP neurons (19), supporting the notion that OLZ might affect energy balance and glucose homeostasis by modulating the activity of these neurons. In this regard, peripheral administration of OLZ in mice is able to acutely induce phosphorylation of hypothalamic AMP-activated protein kinase (AMPK), whose activation has been linked to increased expression of NPY/AgRP. NPY/AgRP neurons have been implicated in the control of glucose homeostasis and, more specifically, the regulation of hepatic insulin sensitivity (20). This study examines whether central nervous system (CNS) delivery of OLZ can affect peripheral glucose homeostasis and insulin action.
RESEARCH DESIGN AND METHODS
Animal model and surgical procedures. Male Sprague-Dawley rats (250–275 g), purchased from Charles River Laboratories (Wilmington, MA), were acclimated to our facilities for 7 days before undergoing surgical catheterization of the left jugular vein and right carotid artery, as previously described (21). A set of rats also received intracerebroventricular cannulae targeting the third ventricle (from bregma-anterior-posterior: −2.2 mm; dorsal-ventral: −7.5 mm from sagittal sinus surface; medial-lateral: 0.0 mm). The jugular catheter served for infusions and the carotid catheter for blood sampling. Rats were allowed to recover for at least 6–10 days after surgery before the clamp studies. The correct placement of the intracerebroventricular cannulae was verified by the induction of a drinking response to 30 ng angiotensin II intracerebroventricularly performed 4 days after the surgery. All animal procedures were approved by the institutional animal care and use committee of the University of Cincinnati.

Olanzapine dosing. The dose of intravenous infusion of OLZ (OLZ-IV group) was selected according to two criteria: 1) the extent of occupancy of the D2 receptors (80–90%) achieved with a single dose (14, 22) and 2) it was experimentally determined to cause only moderate sedation (up to grade 2 [22]). Rats were housed in individual cages in a temperature-controlled environment (22 °C) and were allowed ad libitum access to food and water. Studies were performed during the light phase of the 12:12-h light cycle. Male Sprague-Dawley rats (250–275 g), purchased from Charles River Laboratories (Wilmington, MA), were randomly assigned to vehicle (saline, 0.9%) or artificial cerebrospinal fluid after pH adjustment to 5.5–6.0 as well. An intracerebroventricular (intra-ventricular) bolus of 1.0 µl of OLZ (10 mg/kg, dissolved in saline solution and reconstituted in HCl (0.1 N) was intracerebroventricularly delivered 4 days after surgery. All animal procedures were approved by the institutional animal care and use committee of the University of Cincinnati.

RESULTS
Intravenous infusion of OLZ before and during a hyperinsulinemic-euglycemic clamp. Both OLZ and vehicle groups had similar body weight (vehicle: 317.0 ± 6.3 g vs. OLZ: 316.1 ± 6.0 g), food intake (vehicle: 123.6 ± 4.9 Kcal vs. OLZ: 114.8 ± 5.9 Kcal), and adiposity (epididymal pads, vehicle: 2.165 ± 0.18 g vs. OLZ: 2.198 ± 0.08 g). Intravenous infusion of OLZ transiently increased plasma glucose levels during the basal period compared with rats receiving vehicle [two-way repeated-measures ANOVA group effect, OLZ-IV vs. vehicle: F(1,224) = 6.0, P = 0.02; group × time interaction effect: F(14,224) = 5.7, P < 0.0001] (Fig. 1A). Although the peak in plasma glucose levels was observed 30 min after the start of OLZ administration, there were no differences in the plasma insulin levels during basal or clamp periods between OLZ-IV- and vehicle-treated groups [two-way repeated-measures ANOVA group effect, OLZ-IV vs. vehicle: F(1,70) = 0.61, P > 0.05; group × time interaction effect: F(5,70) = 0.42, P > 0.05] (Fig. 1B). In addition, OLZ increased plasma FFAs, although at the end of the hyperinsulinemic period there was no difference between vehicle- and OLZ-IV-treated groups [two-way repeated-measures ANOVA group effect,
Consistent with the increased EGP, the mRNA levels of hepatic G6Pase (t test = 3.55, P < 0.01) and PEPCK (t test = 2.62, P = 0.01) were higher in the OLZ-IV group compared with control (Fig. 2F).

Since these studies were conducted in male rats, in a separate experiment in mice, we tested whether the acute effect of OLZ on glucose and FFA levels is sex specific. Intraperitoneal injection of OLZ cause significant hyperglycemia and increased FFA levels in both male and females mice (supplemental Fig. 1 in the online appendix, available at http://diabetes.diabetesjournals.org/cgi/content/full/db10-0449/DC1).

**Intracerebroventricular infusion of OLZ before and during a hyperinsulinemic-euglycemic clamp.** Similar to the OLZ-IV studies, intracerebroventricular infusion of OLZ (OLZ-ICV) transiently increased plasma glucose levels during the basal period compared with rats receiving IV vehicle [two-way repeated-measures ANOVA group effect, OLZ-ICV vs. vehicle: F(1,1224) = 12.23, P < 0.01; group × time interaction effect: F(1,224) = 7.57, P < 0.0001] (Fig. 4A). Both groups had similar body weight (vehicle: 329.3 ± 4.4 g vs. OLZ: 325.0 ± 4.5 g), food intake (vehicle: 123.7 ± 2.8 Kcal vs. OLZ: 132.3 ± 4.4 Kcal), and adiposity (vehicle: 2.30 ± 0.11 g vs. OLZ: 2.248 ± 0.09 g). Like in the intravenous studies, OLZ-ICV increased plasma glucose levels in the basal period, with peak values observed 30 min after the bolus of OLZ. Plasma insulin levels during basal or clamp periods were not changed significantly between OLZ-ICV and vehicle groups [two-way repeated-measures ANOVA group effect, OLZ-ICV vs. vehicle: F(1,50) = 1.25, P = 0.28; group × time interaction effect: F(5,50) = 0.54, P = 0.74] (Fig. 3B). Additionally, there were no significant differences in the plasma FFAs between the groups during the basal or hyperinsulinemic periods [two-way repeated-measures ANOVA group effect, OLZ-ICV vs. vehicle: F(1,60) = 3.51, P = 0.08; group × time interaction effect: F(5,60) = 1.10, P = 0.37] (Fig. 3C).

During the basal period, the OLZ-ICV group had a higher \( R_a \) (t test = 2.79, P = 0.01) compared with the vehicle group (Fig. 4A). During the clamp period, the GIR was decreased in the OLZ-ICV group compared with the vehicle group (t test = 4.24, P < 0.001) (Fig. 4B). The decreased insulin sensitivity of the OLZ-ICV group was accounted for by a higher EGP (t test = 3.30, P < 0.01) (Fig. 4D) compared with the vehicle group. However, unlike the OLZ-IV studies, the rate of glucose disposal (\( R_g \)) of the OLZ-ICV group was not changed compared with control (t test = 0.85, P = 0.40) (Fig. 4C).

Moreover, intracerebroventricular infusion of OLZ significantly increased gene expression of G6Pase (t test = 3.18, P < 0.01) and tended to increase PEPCK expression (t test = 1.75, P = 0.09) (Fig. 4E and F).

**Hypothalamic effects of intravenous and intracerebroventricular OLZ.** The phosphorylation of AMPK in hypothalamus of OLZ-IV rats was significantly increased (t test = 2.59, P = 0.01) (Fig. 5A and B), indicating that peripheral acute administration of OLZ activates hypothalamic AMPK signaling. Despite this activation, we did not detect any change in the levels of NPY or AgRP mRNAs (supplemental fig. 2). However, OLZ-ICV significantly increased expression of hypothalamic NPY (t test = 2.88, P = 0.01) and AgRP (t test = 3.27, P < 0.01) mRNA levels compared with vehicle rats without changing the mRNA levels of orexin, MCH, and proopiomelanocortin (Fig. 5C).
In the present study, we show that acute infusion of OLZ either intravenously or intracerebroventricularly induces hepatic insulin resistance. These metabolic alterations are accompanied by hypothalamic activation of AMPK and increased expression of NPY and AgRP. These findings are consistent with the notion that insulin resistance associated with the administration of OLZ could, at least in part, be secondary to its effects on the central nervous system.

Treatment with atypical antipsychotics increases the risk of weight gain, diabetes, and other metabolic disorders in comparison to first-generation antipsychotic drugs (1–3,27). Recent studies (28–30) have also shown that some atypical antipsychotics affect glucose homeostasis before changes in body weight are observed, suggesting that insulin resistance could occur before or independent of any change in adiposity. We showed here that in lean, male rats an acute intravenous infusion of OLZ induced a transient increase of plasma glucose levels (Fig. 1A) in the absence of a compensatory insulin response (Fig. 1B). In several studies, increases in plasma glucose levels have been observed after acute administration of several different atypical antipsychotics in mice. These effects were blocked by a ganglionic blocker, an α2 adrenergic receptor antagonist, or a glucocorticoid receptor antagonist, suggesting a central activation of the sympathetic system (31–33).

Although in humans OLZ-induced obesity and diabetes are not sex specific (34), early studies have preferentially used female rodents because of an apparent stronger sensitivity to OLZ in causing obesity (6,10). Recent findings and our data show that male rats, and mice of both genders, are similarly at risk for OLZ-induced alterations in body weight and glucose homeostasis (supplemental Fig. 1) (8,35).

**DISCUSSION**

**FIG. 2.** Effects of intravenous infusion of OLZ (OLZ-IV, n = 10) or vehicle (n = 8) on (means ± SE) glucose appearance rate (Ra) (A), GIR (B), glucose disappearance rate (Rd) (C), and EGP (D) before and during steady-state hyperinsulinemic-euglycemic clamp condition. Liver (E), G6Pase, and PEPCK (F) mRNA levels (means ± SE) of rats intravenously (iv) infused with OLZ following the hyperinsulinemic-euglycemic clamp. *Statistics denote comparison to vehicle group; t test, P < 0.05.
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FIG. 3. Time course (means ± SE) of plasma levels of glucose (A), insulin (B), and FFAs (C) during basal and hyperinsulinemic-euglycemic clamp periods. Minute 0 represents sampling before a prime-continuous (a bolus of 110 µg and 73.4 µg/h) intracerebroventricular (icv) infusion of OLZ (OLZ-ICV, \( n = 8 \)) or vehicle (\( n = 10 \)). *Statistics denote comparison to respective 0 min and vehicle time-point. Two-way ANOVA followed by Duncan test, \( P < 0.05 \).

OLZ can impair glucose-stimulated insulin secretion after chronic or acute peripheral administration, as shown in hyperglycemic clamp experiments (9,12). We did not detect a change in insulin levels during the basal period of OLZ infusion, despite the fact that intravenous OLZ increased glycemia. The lack of an increase in insulin secretion in response to increased plasma glucose during the OLZ infusion might be related to sympathetic inhibition of insulin release from pancreatic β-cells, as previously suggested (32).

Under hyperinsulinemic-euglycemic clamp conditions, which allowed us to override potential differences in insulin secretion, we found lower rates of exogenous glucose infusion and glucose utilization (GIR and \( R_d \)) and higher EGP in OLZ-IV–infused rats (Fig. 2B–D). These data support the hypothesis that acutely administered OLZ induces insulin resistance. Our observations agree with previous studies showing impairment of insulin action on hepatic glucose production and peripheral glucose utilization after a subcutaneous bolus injection of OLZ (11–13). In addition, here we showed that OLZ-induced insulin resistance was associated with higher gene expression levels of G6Pase and PEPCK, indicating that OLZ impairs the ability of insulin to suppress the expression of rate-limiting enzymes for hepatic glucose output (Fig. 2E and F).

To test the hypothesis that OLZ impairs insulin sensitivity through CNS action, we infused OLZ intracerebroventricularly before and during hyperinsulinemic-euglycemic clamps. Indeed, intracerebroventricular OLZ infusion increased the rate of glucose appearance (\( R_d \)) during the basal period, impaired the ability of insulin to suppress EGP (Fig. 4A and D), and decrease the expression of gluconeogenic enzymes in liver (Fig. 4E and F).

Interestingly, like OLZ-IV, OLZ-ICV markedly impaired hepatic insulin action but did not increase plasma FFAs or impair glucose disposal. Under basal and low insulin levels, OLZ-IV infusion increased plasma FFA levels. However, during hyperinsulinemia, the elevated FFA levels gradually return to control levels (Fig. 1C). This finding agrees with previous reports showing no differences in FFA levels after the hyperinsulinemic-euglycemic clamp condition in rats (11). Nonetheless, in our OLZ-IV studies, we observe a time-dependent and transient increase in FFA levels. Similarly, we found that acute intraperitoneal administration of OLZ in male and female mice increases plasma FFA levels, an effect that was not blocked by pretreatment with a β3-blocker (supplemental Fig. 1D and E). The effect of OLZ on FFA levels has been reported in studies with more prolonged treatment. Healthy men receiving daily OLZ treatment for 8 days display an impaired ability of hyperinsulinemia to reduce plasma FFA levels and increase \( R_d \), in the absence of changes in body weight and adiposity (36). Thus, the reported lack of effect on FFA plasma levels (11) could be due to differences in time of sampling and/or OLZ route of administration.

It is known that elevated plasma FFA levels impair the ability of insulin to suppress hepatic glucose production and stimulate glucose uptake by skeletal muscle (37). However, we observed that only OLZ-IV administration increased plasma FFAs (Fig. 1C) and impaired insulin-stimulated \( R_d \) (Fig. 2C), while OLZ effects on hepatic glucose production occurred regardless of the route of administration and the presence of increased plasma FFA levels (Fig. 2D and Fig. 4D). These data suggest that increased FFA levels do not explain the deleterious effects of OLZ on glucose production.

Our data suggest that the effect of OLZ on FFA and glucose utilization may be mediated by peripheral receptors. In support of this notion, recent studies have shown that OLZ reduced basal and isoproterenol-stimulated release of FFAs in rat adipocytes, as well as glucose uptake (38,39).

Hepatic insulin resistance is a common feature of obesity and type 2 diabetes (37,40) and may result not only from alterations of insulin signaling in the liver but also from impaired insulin action in the brain. Neuronal circuitry responsive to insulin play an important role in modulating hepatic gluconeogenesis in response to
physiologic elevations of plasma insulin (41). In ARC, insulin receptor activation inhibits NPY/AgRP neurons and stimulates proopiomelanocortin neurons in order to control energy homeostasis (42). Furthermore, insulin action on arcuate neurons suppresses hepatic glucose production by a mechanism dependent on phosphatidylinositol kinase–ATP-sensitive K+ channel activation (43).

Intracerebroventricular administration of OLZ increased hypothalamic mRNA levels of NPY and AgRP (Fig. 5C) in rats killed after 2 h of hyperinsulinemic-euglycemic clamps. This result suggests a potential mechanism by which CNS OLZ reduced hepatic insulin sensitivity. Insulin inhibits arcuate NPY and AgRP gene expression and inhibits AMPK phosphorylation/activity (44), whereas inhibition of insulin action in the hypothalamic arcuate nucleus increases the expression of NPY and AgRP (45). Conversely, atypical antipsychotics, including clozapine and OLZ, increase phosphorylation/activity of AMPK (46). In our intravenous studies, OLZ increases hypothalamic AMPK phosphorylation, suggesting that this atypical antipsychotic might counteract the action of insulin on NPY/AgRP neurons by preventing the insulin-mediated inhibition of AMPK. However, unlike intracerebroventricular OLZ, we did not detect increased expression of NPY/AgRP in the OLZ-IV studies. Several studies with peripheral injection of OLZ have failed to find changes in NPY/AgRP levels (6,47), although several lines of evidence show that peripheral OLZ acutely activates ARC neurons (48). We speculate that our finding of increased NPY/AgRP in ICV-OLZ and not in OLZ-IV can be explained by a greater time of neuronal exposure to OLZ in the intracerebroventricular group. Since OLZ can transiently activate AMPK in hypothalamic explants (46), our results in OLZ-IV rats are consistent with an acute activation of

FIG. 4. Effects of intracerebroventricular (icv) infusion of OLZ (OLZ-ICV, n = 8) or vehicle (n = 10) on (means ± SE) glucose appearance rate ($R_a$) (A), GIR (B), glucose disappearance rate ($R_d$) (C), and EGP (D) before and during steady-state hyperinsulinemic-euglycemic clamp condition. Liver (E), G6Pase, and PEPCK (F) mRNA levels (means ± SE) of rats intracerebroventricularly infused with OLZ following the hyperinsulinemic-euglycemic clamp. *Statistics denote comparison to vehicle group; t test, $P < 0.05$. 
AMPK that would later result in increased NPY/AgRP expression. Taken together, our data support the hypothesis that OLZ counteracts the inhibitory action of insulin on hypothalamic AMPK in NPY/AgRP neurons. Intracerebroventricular administration of NPY impairs insulin’s ability to suppress hepatic glucose production (49,50). In addition, selective ablation of the insulin receptor in AgRP-positive neurons leads to hepatic insulin resistance (20). Taken together, these data support the notion that atypical antipsychotics alter hepatic insulin sensitivity by impairing insulin’s action on NPY/AgRP neurons.

In conclusion, we have shown that acute administration of OLZ induces insulin resistance in the absence of changes in food intake and body composition. In agreement with previous studies (9,13), this effect is primarily due to hepatic insulin resistance. These effects are accompanied by the activation of hypothalamic AMPK. Moreover, we showed that CNS delivery of OLZ induces hepatic insulin resistance and activates hypothalamic NPY/AgRP neurons. These data are consistent with the notion that the deleterious effects of OLZ on hepatic insulin action are mediated at least in part by impaired hypothalamic control of hepatic glucose metabolism.

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P.J.F.M. performed experiments and wrote the manuscript. M.H. performed surgeries and clamp studies. S.O. supervised experiments and reviewed/edited the manuscript.

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