Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2010 - 12/31/2013

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA

4. **Grant Contact Person's Telephone Number:** 814 935 1081

5. **Grant SAP Number:** 4100050904

6. **Project Number and Title of Research Project**: 11. Molecular Mechanisms of Olanzapine's Metabolic Side Effects in an Animal Model

7. **Start and End Date of Research Project:** 1/1/2010 - 6/30/2011

8. **Name of Principal Investigator for the Research Project:** Christopher Lynch, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 46,530

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Zhang, Zhiyou	Postdoctoral Scholar	100%	$4,524 (sal+fr)
Xu, Yuping	Research Support Asst	100%	$21,879 (sal+fr)

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Lynch, Chris	PI	< 2%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
NONE		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No_____X___

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes___X_____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert “not funded” in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
Mechanisms of drug side effects related to obesity and diabetes	X NIH ☐ Other federal (specify:_____) ☐ Nonfederal source specify:_____)	5/12/2011	$350,000	$ 317,382

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes_____X____ No_____

If yes, please describe your plans:

I am planning to write a continuing renewal of this project.

12. Future of Research Project. What are the future plans for this research project?

We are currently focused on identifying the target of the acute actions of the antipsychotics that lead to an apparent block in the use of glucose as a fuel. To this end we are performing 13C-glucose flux studies in our model system. We anticipate a genomic response to these drugs and so have performed Exome Next-Gen sequencing in muscle at different times after drug. Another goal is to identify the factors associated with the increase deposition of fat in adipose tissue.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				1

Female				
Unknown				
Total				**1**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				1
Unknown				
Total				**1**

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				1
Other				
Unknown				
Total				**1**

14. **Recruitment of Out-of–State Researchers**. Did you bring researchers into Pennsylvania to carry out this research project?

    Yes_____ No___X_____

    If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. **Impact on Research Capacity and Quality**. Did the health research project enhance the quality and/or capacity of research at your institution?

    Yes____X_____ No____ _____

    If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

    Funding for this project enabled research training for a postdoctoral fellow who will contribute to the pool of qualified investigators in future years. In addition, the preliminary data that we obtained was crucial in getting my NIH grant funded and this has helped to further strengthen the base for health research at Penn State Hershey.

16. **Collaboration, business and community involvement.**

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No_____X____

If yes, please describe the collaborations: Not until after the NIH grant was in place

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No_____X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic

plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

The research seeks to examine the mechanisms of specific aspects of the metabolic side effects of atypical antipsychotics leading to lipid abnormalities and satiety.

Aim 1. Determine the effect of olanzapine on FFA oxidation (measure FFA uptake and Acyl carnitine species in vivo) and uncover the role of malonyl CoA in this effect and the underlying mechanism (AMPK activation, ACC inhibition, reduced anaplerosis)

Aim 2. Determine the role of cAMP in the anti in vivo lipolysis effect of atypical antipsychotics.

Aim 3. Examine the mechanism of leptin lowering

Atypical antipsychotics (olanzapine, clozapine, risperidone) have a number of adverse metabolic side effects including increased thirst and hunger, body weight gain, obesity and diabetes. Some of the diabetes has been sufficiently severe as to lead to amputation. The change in body weight occurs quite quickly. Because schizophrenia diagnoses peak in the 17-early twenties when a person's looks may be particularly important in social interactions, these weight gain side effects frequently seriously interfere with treatment compliance. This is a problem not only for the obvious reason of untreated psychiatric disease, but because of the well-known phenomenon of reduced treatment effectiveness of the antipsychotics when there are treatment lapses. That means if treatment is voluntarily stopped, the efficacy of the drugs upon re-initiation of treatment appears to wane when treatment is reinitiated. The reason for this is not known. Another issue is that while some of the "atypicals" have reduced metabolic side effects, efficacy for psychiatric endpoints seems to correlate nearly directly with the propensity of the individual drugs to give rise to the metabolic side effects.

The goal of this project was to identify the mechanism of some acute metabolic side effects of the atypical antipsychotics that had been observed in humans and our animal model. During the course of the funded studies, we completed aims 1 and 2 but, shortly after the project was funded, the rationale for doing aim 3 was abrogated. That aim was to investigate the mechanism of leptin lowering that we had observed in rodents. We thought that could help explain increased food intake in humans. Our observation was consistent with discussion in one clinical study, which indicated that the increases in leptin they observed were not as large as they expected for the increased adiposity that subjects taking olanzapine experienced. However subsequent studies refuted that finding. Furthermore additional studies in rodents (and dogs by another group) failed to demonstrate frank increases in food intake except as corrected for reduced physical activity (vance paper). Most of the

subsequent studies have reported increased not decreased leptin secretion. Therefore, the rationale for studying the leptin lowering that we observed in rats despite increased weight gain appeared to be a phenomenon restricted to the animal model so we decided not to pursue it.

Aims 1 and 2 were investigated and the completion of these studies led to a new NIH grant that we are currently in the process of trying to renew. The aim 1 studies were completed and published in two papers that appeared in Schizophrenia Bulletin (5yr impact factor ~9) and Molecular Psychiatry (5yr impact factor of ~14.3) (1; 2).

We will first present the Results and then the Methods used.

Results

Aim 1

Several pieces of data demonstrated that olanzapine caused a rapid and sustained metabolic switch from glucose to FFA utilization. For example, as shown in Table 1, plasma glycerol and free fatty acids (NEFA or FFA) dropped after acute and chronic administration of olanzapine, whereas there was a rise in the plasma glucose. We next initiated a number of acute studies to further investigate this. It was striking that in contrast to traditional type 2 or type 1 diabetes where glucose and FFA are elevated, after olanzapine there was hyperglycemia but FFA was lower. In a diabetic state, the lack of insulin signaling causes decreased glucose disposal and increases hepatic glucose output, but it also decreases lipogenesis and increases sensitivity to lipolytic stimuli. The elevation of FFA is necessary to provide a secondary fuel for the muscle and heart, two insulin sensitive tissues. Olanzapine appears to prevent the utilization of glucose by a number of tissues (decreased whole body glucose utilization, causes an inappropriate switch (i.e., even in the fed state) to use of fat as a major fuel and increases lipogenesis and decreases lipolysis (1; 2).

The fact that fat utilization increases after olanzapine is shown by several pieces of evidence. One of these is from indirect calorimetry (Fig 1A-C. Using indirect calorimetry, we measured the Respiratory Exchange Ratio (RER) in animals following acute olanzapine treatment. RER is the ratio of carbon dioxide produced to oxygen consumed (RER = VCO_2/VO_2) and reflects the metabolic fuel being used for energy. RER fluctuates with normal feeding and fasting. It approaches a value of 1.0 when carbohydrate is oxidized and a value of 0.7 indicating pure lipid oxidation. As seen in Figure 1A or1B, almost immediately following olanzapine gavage (indicated by arrows) there was a robust decrease in RER compared to control rats whose RER increased normally during dark cycle. In Fig 1B the animals were in the ad libitum fed state. The olanzapine-mediated decline in the RER slowly returned to control levels over the course of the dark cycle with a time course that was consistent with the half-life of olanzapine in rats (~2h). When another dose was provided at shortly after the beginning of the light cycle (Fig 1B), the next dose of olanzapine again elicited another decrease in the RER, which again returned to control values over the same time course. The 24 hr food intake did not differ between control and olanzapine treated animals [Con: 27.2 ± 1.0 g, (n= 12) *vs.* Olz: 26.3 ± 0.9 g, (n=12)] during this 24 hr period. Experiments continued for the 36 hours in a subset of the animals to determine if the robust

RER decrease was a short-lived phenomenon, but, as seen in Figure 3A, a third dose of olanzapine at 25 hours was again able to elicit a decrease in RER comparable to that observed after the first dose. On average, RER in both the dark and light cycles was significantly lower in olanzapine animals compared to control, due to the robust decreases after drug administration. Consistent with the changes in plasma lipids, drug-treated animals appear to be burning fats instead of carbohydrates, as reflected by lower RER.

The effect of olanzapine on RER was also examined after food-restriction in rats acclimated to the metabolic cages (Fig 1A). Ad libitum fed animals were given olanzapine or vehicle and re-placed in calorimetric cages without food. RER declined after food deprivation in control animals as expected. However in the olanzapine group it was already significantly lower by the first measurement and declined subsequently but not below values ultimately achieved by the food deprived Control group. By the end of the dark cycle both experimental groups had been food-restricted for ~12 hours and, as expected, the RER in each groups was ~0.7 indicating that animals were predominately using fat for fuel. Upon repeat gavage at the beginning of the light cycle, there was no further decline in RER in the olanzapine treated group (Fig 1B).

In a third experiment, the effect of olanzapine in food-deprived rats was examined during re-feeding (Fig 1C-D). Animals were food-restricted for 14 hrs. and re-fed approximately 30 minutes after oral olanzapine or vehicle administration. RER in the 14 hr food-deprived (a.k.a., fasted) rats (Fig 1C) was approximately 0.7. Olanzapine significantly blunted the rate of rise in RER with refeeding (Fig 1C), even though food intake in the first 2 hours was the same between groups (Figure 1D). Consistent with previous studies, 12 hr food intake, like 24 hr food intake, did not differ between control and drug-treated animals (Fig3D). Overall, olanzapine causes a rapid and robust decrease in respiratory quotient that appears to reflect a 'switch' from oxidation of mixed fuels, but mostly carbohydrate (RER =~ 0.9) to oxidation of lipids (RER = 0.7). Similar results were observe in mice with olanzapine and other side effect prone atypical antipsychotics (2).

At the doses of drug used in Fig 2, olanzapine did not decrease the 24 hr oxygen consumption values; although in later studies we determined that at higher doses VO_2 was impaired as the doses of drug escalated.

The increase in the fat oxidation as suggested by calorimetry was consistent with the data in table 1, however to provide further evidence that olanzapine was increasing fatty acid utilization we measured tissue specific FFA flux using an [^{125}I] labeled fatty acid, [^{125}I] beta-methyl-iodo-phenyl-pentadecanoic acid ([^{125}I]-BMIPP). [^{125}I]-BMIPP was given as a bolus intravenous injection in the morning shortly after the beginning of the light cycle to animals that had ad libitum access to food. Fed rats were used because this is when NEFA concentrations were the same as opposed to after overnight food-restriction when there are be large differences between NEFA in control and drug groups (1; 2). As seen in Figure 3A, olanzapine increased NEFA uptake, there was a +120% change from control (%CFC) in gastrocnemius and soleus muscles. Two tissues with normally high rates of fatty acid oxidation, namely the liver and kidney, showed similar increases in NEFA uptake, approximately 100-120%CFC (Fig 3B). However, another tissue with already high rates of

fatty acid oxidation, the heart, showed no significant difference in uptake despite increased work shown earlier Fig 3A. Compared to muscle and heart, GI and skin tissues are not insulin dependent with respect to glucose uptake but nevertheless are responsible for a significant fraction of the whole body glucose utilization in normal rats, ~16-40% depending on metabolic state. NEFA uptake was also significantly increased, 80-120%CFC, in adipose tissue depots (Fig 3D), two sections of the small intestine, proximal duodenum and terminal ileum, as well as skin (Fig 3C). Brain uptake of NEFA flux was also measured. As expected, brain NEFA uptake was too small to determine any effect of olanzapine reliably (<0.1 nmol/g tissue/min). Thus, within most peripheral tissues, with the exception of the heart, there appears to be an apparent switch to using fatty acids as the principle metabolic fuel rather than carbohydrates or amino acids based on calorimetry and FFA flux studies. Olanzapine treatment is accompanied by a generalized increase in NEFA metabolic rate.

Other experiments were performed to evaluate the mechanism underlying the increase in fat oxidation we observed after olanzapine treatment. The rate limiting step for fatty acid oxidation is the activity of carnitine palmitoyltransferase I (CPT1). The activity of CPT1 is regulated by changes in the cellular concentration of malonyl-CoA. We found that gastrocnemius malonyl-CoA concentrations were reduced by ~56% following acute olanzapine treatment (Table 2). Such differences in malonyl-CoA are similar to those observed in comparisons of starved and refed rats, which have comparable changes in RER (3).

Olanzapine's effect on the malonyl-CoA concentration could be due to a direct inhibition of acetyl Co-A carboxylase (ACC) or alteration in AMP kinase (AMPK) pathway activity. Since ACC inhibitors vary widely in their structures, we examined the ability of olanzapine to directly inhibit recombinant human ACC1 and ACC2 along with two known inhibitors, Soraphen A and CP-640186 (Fig 4). While Soraphen A and CP-640186 inhibited ACC1 and ACC2 *in vitro* with expected IC_{50}s, olanzapine had no appreciable effect over relevant and even toxic concentrations. We also detected no change in fed gastrocnemius AMP kinase activity due to acute olanzapine treatment based on phospho-specific pT172 AMPK immunoreactivity (Fig 5).

ACC is also regulated by substrate availability, i.e., cellular citrate arising from anapleurosis to the TCA cycle. Gastrocnemius citrate concentrations, measured in a separate cohort of animals (Table 2), were significantly depressed by olanzapine, as were other measured TCA intermediates in the first span of the TCA cycle including α-KG (~26% decrease) and succinyl-CoA (51% decrease). Surprisingly, olanzapine had no effect on intermediates in the next span of the TCA cycle: succinate, fumarate and malate (Table 2, oxaloacetate, cis-aconitate and isocitrate, could not be detected). Olanzapine also did not acutely affect free CoA, acetyl-CoA, pyruvate or lactate concentrations in muscle. Consistent with fed plasma alanine concentrations (Fig 1), fed gastrocnemius alanine was not different after olanzapine. Anapleurotic amino acids were also affected by acute olanzapine. Concentrations of amino acids related metabolically to a-ketoglutarate declined, including Glutamate and Glutamine (~20%), Proline (~30%), Ornithine (~30%) and Citrulline (30%). The decrease in muscle succinyl-CoA was associated with elevated Val but not Leu/Ile concentrations; however BCAA metabolic intermediates accumulated (see below). Other amino acids, Arg, Asx, Gly,

His and Met were not significantly affected. However, Phe was increased whereas its metabolite Tyr was significantly decreased by olanzapine compared to control values.

Acyl-carnitines serve multiple functions including as buffers for corresponding acyl-CoAs. Buffering activity may help preserve CoA levels for fatty acid oxidation and energy production. Thus a rise in these acyl-carnitines may reflect increases in their corresponding acyl-CoAs due to either accelerated or impaired metabolism. Acyl-carnitines from fed gastrocnemius of control and olanzapine-treated rats were also measured (Table 3). No change in acetyl-carnitine (C2) was observed consistent with the lack of effect on acetyl-CoA concentrations. However, a significant increase or trend for increase in several other short chain acyl-carnitines in response to olanzapine treatment was detectable. For example, propionyl-carnitine (C3) was increased ~28%. C3 can be derived from several amino acids including BCAAs (4; 5), gut propionate and odd-chain fatty acids and the corresponding propionyl-CoA can yield succinyl-CoA. Several species associated with BCAA to succinyl-CoA pathways (4; 5) were elevated: C4/Ci4 (includes isobutyryl-carnitine from Val) and C5s (includes isovaleryl-carnitine from Leu, tiglyl-carnitine from Ile and methylbutyryl-carnitine from Ile). Consistent with the decrease in Tyr, there was a trend for a decrease in the carnitine species arising from glutyryl CoA (C5-DC).

Table 3 shows that olanzapine also elicited a 43-78% rise in the muscle concentrations of long-chain species that most likely arise from 3-hydroxylation of palmitoleic, palmitic, oleic and linoleic CoA esters during fatty acid metabolism. Consistently, there was also a trend ($p= 0.055$) for a peak that probably represents 3-hydroxy-tetradecenoyl carnitine (C14-OH). Other acyl-carnitine species that can also accumulate in chronic diabetes and "mitochondrial overload" were not impacted by acute treatment (e.g., unmodified long-chain and medium-chain fatty acid carnitines and hydroxylated medium-chain acyl-carnitines, Table 3). Figure 6 shows a graphical representation of the above findings with olanzapine.

Aim 2.

We measured adipose tissue cAMP before and during an isoproterenol challenge test in SD rats. Under these conditions an obvious impairment in lipolysis was evident (Fig 7). However no change in cAMP in adipose tissue frozen powders was detected using an assay kit from CisBio (data not shown).

Methods

Animals. The animal facilities and protocols were reviewed and approved by the Institutional Animal Care and Use Committee of The Pennsylvania State University College of Medicine. Male and female Sprague-Dawley rats (~200-225 g) were purchased from Charles River Laboratories (Cambridge, MA). Male C57Bl/6J mice were purchased from The Jackson Lab (Bar Harbor, ME). All animals were maintained on a 12:12h light-dark cycle with food (Harlan-Teklad Rodent Chow, no. 2018) and water provided *ad libitum*.

Chronic Dosing. Olanzapine was administered with ramped dosing as previously described (6). An exception was that on the morning of day 28, after a 14h fast, a half dose of

olanzapine, 6 mg/kg, was given to animals by oral gavage 2h before blood sampling for measurement of FFA and glycerol or insulin tolerance testing.

Acute Dosing. In acute studies, endpoints were measured after two doses of vehicle (water, pH 5.5) or olanzapine (10 mg/kg). The first dose was administered before the start of the dark cycle at approximately 1800h. The following morning a second dose of vehicle or olanzapine was administered typically between 0700 and 0800h two hours prior to the beginning of any experiment or blood/tissue sampling. This regimen is based on our previous study (6) and the maximum dose of olanzapine (10 mg/kg) was chosen because it produced a consistent elevation of blood glucose in pilot studies. In the calorimetry time course studies, drug was provided at the time indicated in the figure in fed or food-deprived animals as indicated.

Insulin Tolerance Tests (ITT). ITTs were performed after either 5h (Acute) or 14h (Chronic) of food-deprivation (6) following i.p. injection of 0.75 U/kg, Humulin-R (Lilly; Indianapolis, IN).

Glucose Infusion Rate (GIR) During Hyperinsulinemic Euglycemic Clamp. GIR was measured as previously described (7) using a dose of insulin that approximated fed insulin concentrations. During the basal period (t = -120 to 0 min), saline was infused through the venous catheter and a tracer amount of tritiated glucose (3-[3H]-glucose; Perkin-Elmer, Waltham, MA) was infused as a primed-continuous infusion (10 μCi bolus, 0.2 μCi/min) through the hybrid venous catheter for measurement of basal hepatic glucose output. At time zero (t = 0), a primed-continuous insulin infusion (75 mU/kg bolus, 1 mU/kg/min, 0.3% BSA) was started and glucose (20% dextrose) was co-infused to maintain euglycemia (~100 mg/dl).

Indirect Calorimetry. Respiratory exchange ratio (RER) in rats and mice after acclimation was calculated by indirect calorimetry (Oxymax, Columbus Instruments) as previously described (7; 8).

Tissue FFA Uptake. Tissue specific FFA uptake was measured using the non-metabolizable fatty acid analog, [^{125}I]-BMIPP, as previously described and validated (12). Four days after catheter implantation rats were dosed with olanzapine or vehicle according to the acute dosing protocol. At approximately 0700h, a tracer amount of [^{125}I]-BMIPP (10 μCi) was given as an intravenous (i.v.) bolus (t = 0 min). Serial blood samples (~250 μl) were collected (t = 2, 5, 10, 20, 30, 40) to determine the AUC for plasma [^{125}I]-BMIPP during the *in vivo* labeling period. After final blood samples were collected (t = 40 min), animals were euthanized and tissues (i.e. gastrocnemius, soleus, heart, liver, kidney, gut, skin, brain) freeze-clamped in liquid nitrogen. Total [^{125}I]-BMIPP activity was measured in plasma (25 μl) and whole-tissue (~100 mg) for calculation of FFA metabolic rate (R_f).

Analytical Procedures and Clinical Chemistry Measurements. Blood glucose measurements were made with an Ascensia® Contour® blood glucometers (Bayer Healthcare LLC; Mishawaka, IN). Insulin concentrations were determined using a commercial ELISA kit for rat insulin (Mercodia; Uppsala, Sweden). The following plasma metabolite concentrations

were made using colorimetric assays: plasma glucose (Thermo Scientific, Waltham, MA), FFAs (Wako Diagnostics, Richmond, VA), glycerol (Cayman Chemical, Ann Arbor, MI) and beta-hydroxybutyrate (Stanbio Laboratory, Boerne, TX). Plasma triglycerides and lactate were measured using the DT60II module of the Vitros Clinical System (Ortho-Clinical Diagnostics, Rochester, NY). Branched-chain amino acids and plasma alanine concentrations were measured using enzyme-linked reactions (13). Tissue Co-A species were measured by HPLC as previously described (14). Metabolomic profiling of tissue amino acids (15), organic acids (16) and acyl-carnitines (17) were determined as previously described.

Calculations. The FFA metabolic rate, R_f, was calculated by taking the total tissue counts of [^{125}I]-BMIPP and dividing by the AUC of [^{125}I]-BMIPP during the 40 min *in vivo* labeling period and multiplying by the mean plasma FFA concentration (12). Cardiac minute work (dyne·cm/min) was calculated as the product of pulse (beats/min), stroke volume (cm^3), and arterial pressure (mmHg) using the conversion factor of 1 mmHg = 1332 dyne/cm^2. An index of cardiac energy expenditure, the 'double-product', was calculated as the product of pulse (beats/min) and arterial pressure (mmHg).

Statistical Analyses. For all results, data are expressed as the mean ± standard error. In the text, increases relative to control are presented as % change from control, in which no change would be 0%. To calculate statistical significance (P<0.05), Student's t-test or one-way analysis of variation (ANOVA) with Bonferroni's multiple comparison post-test was used when appropriate. Sample size for each group is presented in the respective figure legends. Asterisks indicate at least a certain P value as follows: *P<0.05; **P<0.01; ***P<0.001. All statistical analyses and data manipulations were made using GraphPad Prism and InStat computer programs (GraphPad Software, San Diego, CA).

TABLES AND FIGURES

Table 1. Plasma FFA, Glycerol, Insulin Tolerance Test Areas Under-the-Curve (ITT-AUC), and Euglycemic Clamp Glucose Infusion Rate after Chronic or Acute Olanzapine Treatment in male, Sprague-Dawley Rats.

				Condition	
Treatment Day	**Dose** *mg/kg/day*	**Food Restriction**	**Endpoint**	**Control[a]**	**Olanzapine[a]**
28 (Chronic)	Ramp, 4-12[b]	14h	FFA	0.91 ± 0.05	0.58 ± 0.04***
			Glycerol	1.79 ± 0.13	1.34 ± 0.12*
			ITT-AUC	6,226 ± 564	3,797 ± 569**
2 (Acute)	4	5h	FFA	0.63 ± 0.05	0.38 ± 0.02***
			Glycerol	1.95 ± 0.08	1.61 ± 0.05**
			ITT-AUC, GIR	6,054 ± 344 81.4 ± 5.3	4,436 ± 415** 43.2 ± 5.5***

[a]Values are means ± SE; n= 10-12. Asterisks indicate statistical difference from Control group (*P<0.05, **P<0.01, ***P<0.001). Parameters reported in SI Units: FFA, mM; glycerol, mM, (GIR) Glucose Infusion Rate, mmol/kg/min, ITT-AUC (Time ! % Change from Baseline Glucose)

More information about this table can be found in (1)

Table 2. Effect of acute olanzapine on intermediary metabolites in fed rat gastrocnemius[a]

Metabolite	Control	Olanzapine	P value
	nmol/g protein		
Free Co-A	176 ± 40	177 ± 29	
Acetyl-CoA	525 ± 51	491 ± 57	
Malonyl-CoA,	36 ± 6.3	16 ± 4	0.017
Citrate	643 ± 36	533 ± 28	0.0024
α-Ketoglutarate	6622 ± 290	4953 ± 278	0.0007
Succinyl-CoA	47 ± 8.6	23 ± 5.1	0.031
Succinate	573 ± 91	762 ± 120	
Fumarate	2535 ± 129	2480 ± 140	
Malate	4954 ± 133	4990 ± 251	
	***μmol*/g protein**		
Pyruvate	29 ± 3	32 ± 5	
Lactate	167 ± 11	183 ± 10	
Ala	15 ± 1	16 ± 1	
Arg	2.9 ± 0.17	2.7 ± 0.20	
Asx	3.25 ± 0.25	3.65 ± 0.32	
Cit	2.05 ± 0.11	1.5 ± 0.08	0.004
Gly	27 ± 2	26 ± 1	
Glx	15.8 ± 0.80	13.0 ± 0.65	0.039
His	2.56 ± 0.11	2.69 ± 0.11	
Leu/Ile	5.2 ± 0.22	5.1 ± 0.19	
Met	0.53 ± 0.021	0.53 ± 0.024	
Orn	0.75 ± 0.040	0.53 ± 0.027	0.003
Phe	1.0 ± 0.05	1.2 ± 0.05	0.012
Pro	4.3 ± 0.2	2.9 ± 0.2	0.001
Tyr	1.6 ± 0.01	1.3 ± 0.5	0.024
Val	1.37 ± 0.057	1.58 ± 0.056	0.011

All data represent the mean ± S.E. P values < 0.1 are shown. [a]Gastrocnemius samples (n=8/grp) were analyzed for Coenzyme-A (Co-A) species and other metabolites were measured from a separate cohort of rats not infused with radioactivity (n=10/grp).

Table 3. Effect of acute olanzapine on acyl-carnitines in fed rat gastrocnemius[a]

Acyl-Carnitine	Control	Olanzapine	P value
	nmol/g protein		
C2	1238 ± 92	1150 ± 82	
C3	14.8 ± 1.08	18.9 ± 0.92	0.02
	pmol/g protein		
C4/Ci4	3522 ± 257	4866 ± 776	0.047
C5:1	1653 ± 95	1975 ± 120	0.070
C5's	3952 ± 371	9427 ± 1285	0.007
C4-0H	3902 ± 301	3953 ± 260	
	nmol/g protein		
C6	758 ± 87	1132 ± 176	
C5-0H/ C3-DC	14,003 ± 858	14,638 ± 609	
Ci4-DC/ C4-DC	5147 ± 316	4638 ± 328	
C8:1	259 ± 23	265 ± 24	
C8	355 ± 33	401 ± 47	
C5-DC	237 ± 22	181± 21	0.09
C6:1-DC/ C8:1-OH	128 ± 17	107 ± 20	
C6-DC	114 ± 25	158 ± 24	
C10:3	164± 23	230 ± 26	
C10:2	174 ± 24	178 ± 29	
C10:1	433 ± 99	377 ± 40	
C10	198 ± 32	140 ± 23	
C7-DC	62 ± 12	51 ± 7	
C8:1-DC	76 ± 13	56 ± 14	
C10-OH/ C8-DC	345 ± 59	479 ± 118	
C12:1	176 ± 28	163 ± 24	
C12	313 ± 54	211 ± 33	

Acyl-Carnitine	Control	Olanzapine	P value
	nmol/g protein		
C12-OH/ C10-DC	431 ± 69	570 ± 89	
C14:2	313 ± 58	315 ± 43	
C14:1	541 ± 135	530 ± 94	
C14	1447 ± 262	1188 ±200	
C14:1-OH/ C12:1-DC	971 ± 146	1186 ± 170	
C14-OH/ C12-DC	911 ±142	1269 ± 160	0.055
C16:2	457 ± 74	427 ± 50	
C16:1	1230 ± 164	1180 ± 117	
C16	3941 ± 454	3706 ± 366	
C16:1-OH/ C14:1-DC	1779 ± 252	2596 ± 336	0.030
C16-OH/ C14-DC	1849 ± 192	2650 ± 327	0.024
C18:2	3708 ±404	4196 ±409	
C18:1	4765 ± 761	4214 ± 412	
C18	2067 ± 183	2041 ± 105	
C18:2-OH	2531 ± 273	4517 ± 620	0.005
C18:1-OH/ C16:1-DC	5642 ± 581	8632 ± 845	0.002
C18-OH/ C16-DC	652 ± 74	795 ± 82	
C20:4	858 ± 113	973 ±92	
C20	100 ±14	115 ± 15	
C20:1-OH/ C18:1-DC	96 ± 14	87 ± 17	
C20-OH/ C18-DC	110 ±12	117 ±13	
C22	46 ± 8.1	60 ± 6.2	

All data represent the mean ± S.E. P values < 0.1 are shown (n=10/grp). More information about this table can be found in (1)

Figure 1

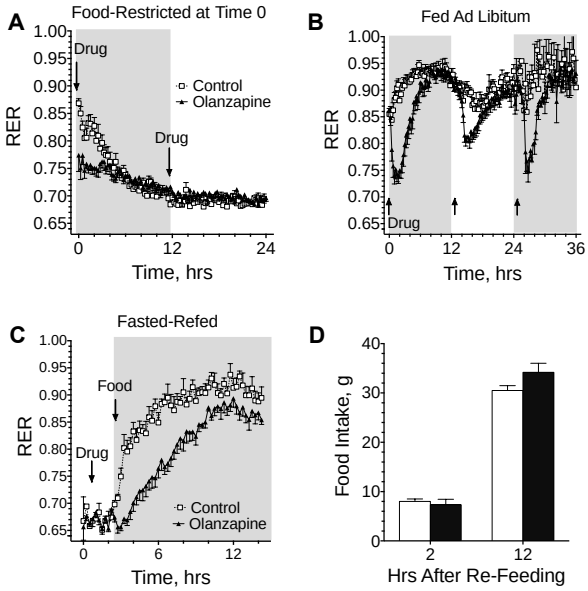

Figure 1. Effects of Olanzapine on respiratory exchange ratio in ad libitum fed, food-restricted, and re-fed animals. Background shading or lack thereof indicates the dark and light cycles, respectively. Arrows indicate the time of Olanzapine gavage (10 mg/kg). (A) Animals were placed in metabolic chambers and subsequently received Olanzapine via gavage while retaining ad libitum access to food and water. Respiratory exchange ratio (A) was calculated based on expired carbon dioxide and oxygen consumed (RER = VCO_2 / VO_2). Each cage was measured for one minute every 15 minutes for 24 hours (n = 12). A subset of animals remained in the cages for up to 36 hours for additional measurements. (B) In another set of experiments, ad libitum fed animals were placed in metabolic chambers and then food-restricted. RER was measured over the 24hr period. In a third experiment (C-D), animals were 14hr food-restricted and gavaged with Olanzapine 45 minutes prior to the start of the dark cycle. Re-feeding began approximately 30 minutes after drug dosing. (C) RER and food intake (2 and 12 hour) was measured during the experiment (n = 6). All data represent the mean ± S.E. Black bars with asterisks indicate significant differences from control (*P<0.05).

Fig 2

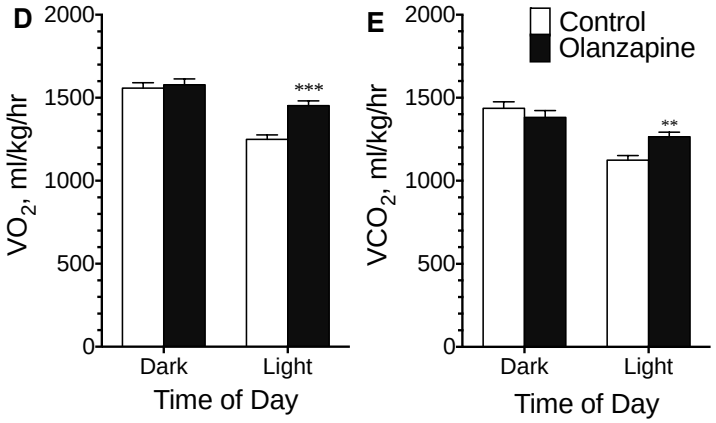

Figure 2. Energy expenditure and locomotor activity following acute olanzapine administration. Animals were placed in specialized chambers to measure locomotor activity and energy expenditure using indirect calorimetry. Following acclimation, olanzapine (10 mg/kg) or vehicle solution was administered by oral gavage. Animals retained *ad libitum* access to food and water for the duration of the experiment. (D) Average VO_2 and (E) Average VCO_2 for the dark and light cycles were calculated. All data represent the mean ± S.E. (n = 12), asterisks indicate significant differences (***P<0.001, **P<0.01). [Control = White Boxes, Olanzapine = Black Triangles] These figures are from (1).

Fig 3

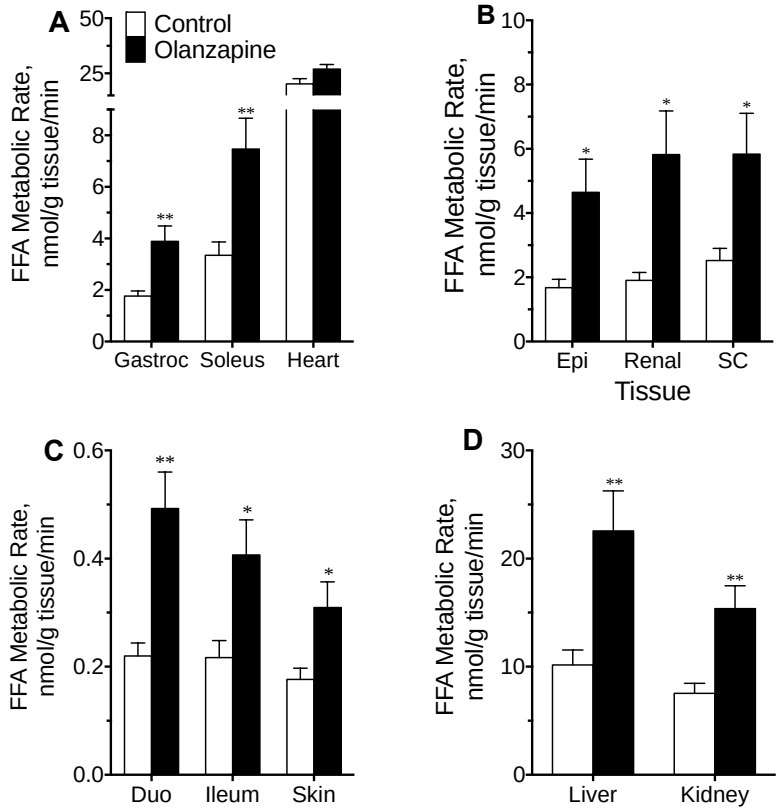

Fig 3. Tissue non-esterified fatty acid uptake after Olanzapine administration. The non-metabolizable, fatty acid analog tracer [^{125}I]-BMIPP was used to measure non-esterified fatty acid uptake in fed animals with ad libitum access to food and water. At least 4 days prior to experiments, arterial and venous catheters were implanted in male rats. On the second day of Olanzapine (10 mg/kg) administration, animals received a bolus intravenous injection of BMIPP and serial blood samples were drawn for calculation of plasma activity and non-esterified fatty acid concentration during a 40-minute in vivo labeling period. Tissues samples were counted for radioactivity and calculation of non-esterified fatty acid uptake (NEFA Metabolic Rate = nmol/ g tissue / min). Tissues sampled included (A) skeletal and cardiac muscle, (B) Adipose tissue depots: epididymal (Epi), perirenal (Renal), and subcutaneous (SC); (C) proximal duodenum (Duo), terminal ileum, and skin and (D) liver and kidney. Asterisks indicate significant differences (*P<0.05, **P<0.01) compared to control. Data represent the mean ± S.E. (n = 8)

Fig 4.

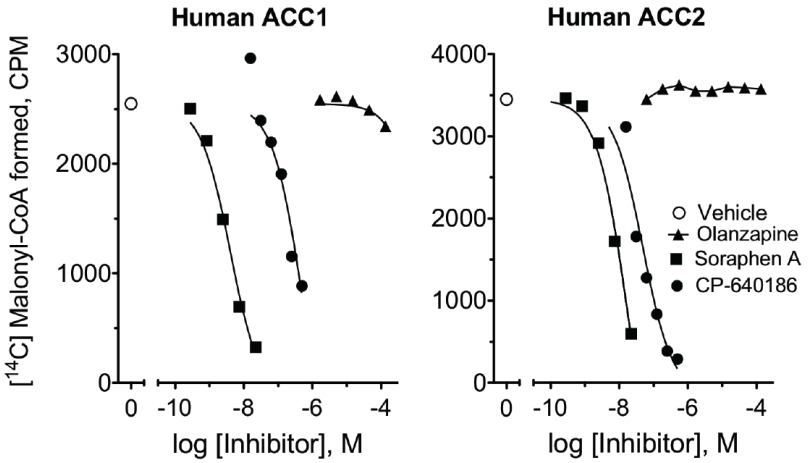

Fig 4. *In vitro* inhibition assay of human acetyl-CoA carboxylase isoforms *h*ACC1 and *h*ACC2. Overall ACC activity in the *h*ACC preparations was measured by following incorporation of [^{14}C]-bicarbonate into malonyl-CoA. Potential inhibition of *h*ACC1 and *h*ACC2 by olanzapine, with concentrations of olanzapine up to 135 µM, and inhibition by the known ACC inhibitors, Soraphen A and CP-640186, was measured.

Fig 5

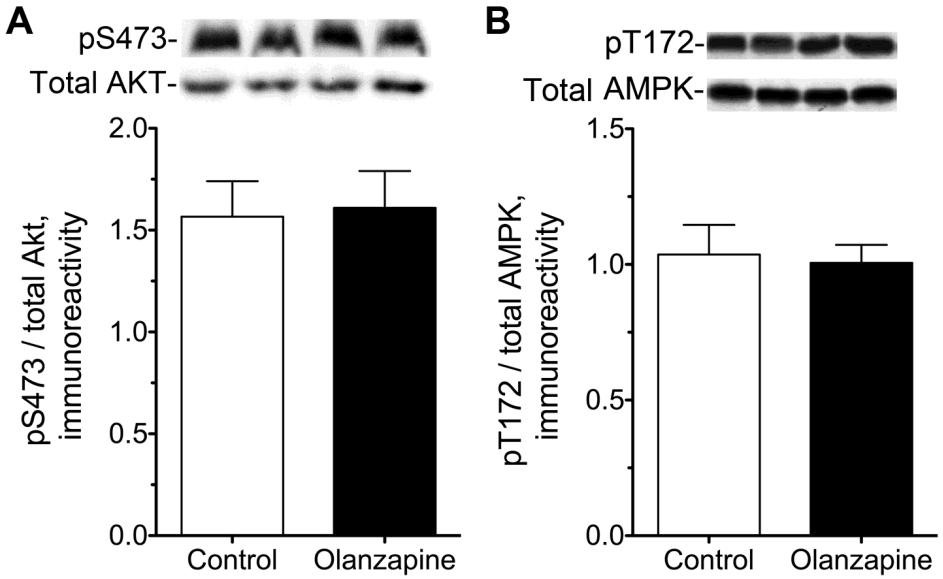

Figure 5. Effect of olanzapine on AKT and AMPK phosphorylation in skeletal muscle of *ad libitum* fed male rats. Gastrocnemius tissues were excised and immediately freeze-clamped approximately 2h after vehicle or olanzapine treatment. Tissue homogenates were subjected to Western blotting and quantified using chemiluminescence to measure the activity (ratio of phosphorylated (p) isoform to total protein isoform) of (A) AKT (Ser^{473}) (B) AMPK (Thr^{172}). Representative images from actual blots are shown along with relative quantification representing the mean intensity ± S.E. (n = 8).

Fig 6

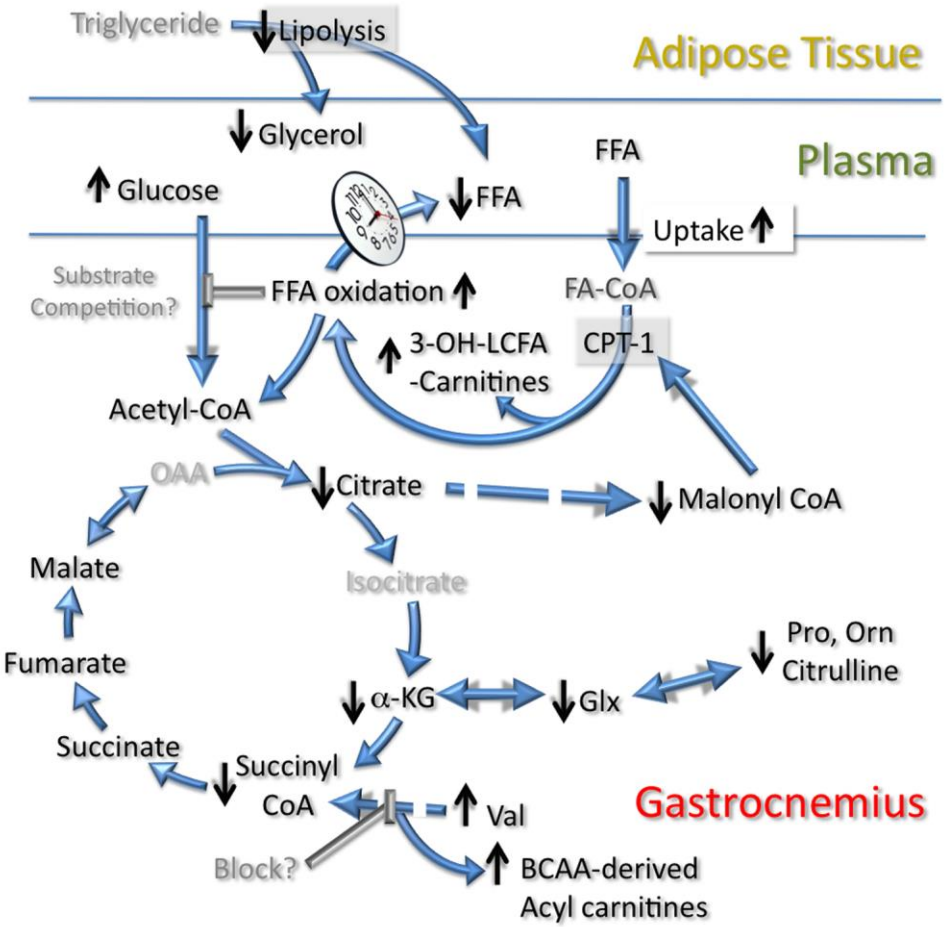

Figure 6. Schematic representation of findings. Olanzapine lowered fasting plasma glycerol implicating impaired lipolysis however FFA was depressed lower. FFA lowering appears secondary not only to impaired lipolysis but also increased uptake FFA by most peripheral tissues and elevated lipid oxidation. The key regulator of fat oxidation was decreased along with muscle TCA cycle intermediates and anapleurotic metabolites contributing to the first strip of the TCA cycle. Measured metabolites are indicated by black text.

Fig 7.

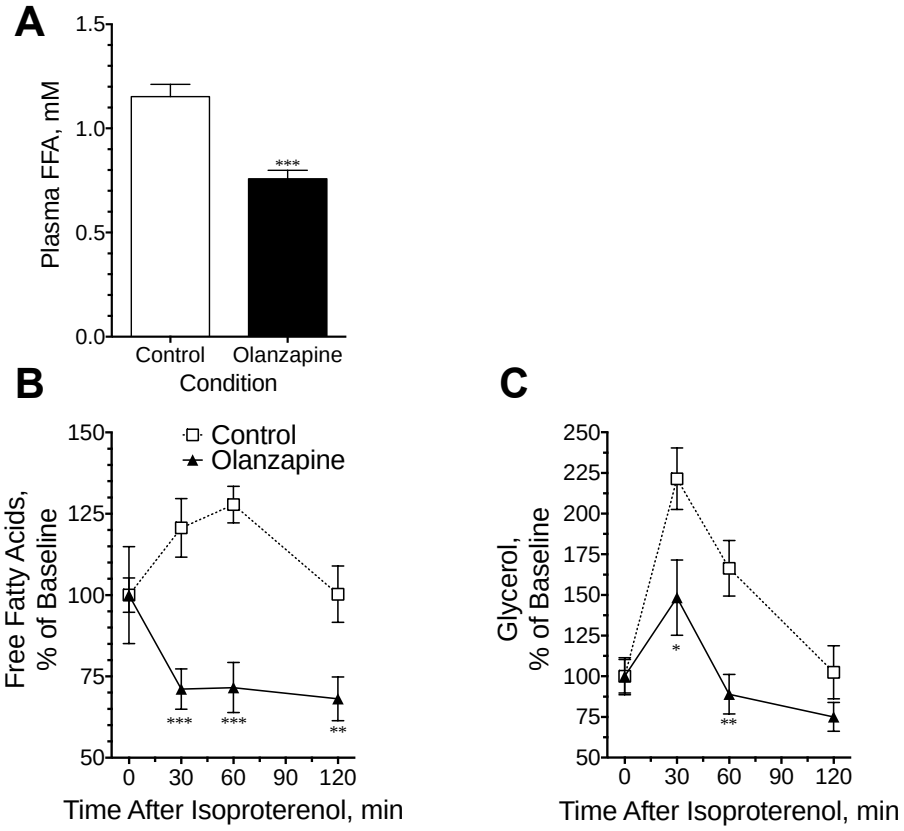

Figure 7. Acute effects of olanzapine on circulating FFA, adipose tissue uptake, and mobilization of FFA and glucose in response to an isoproterenol challenge. (A) Plasma FFAs were measured in 14h food-restricted animals following olanzapine (10 mg/kg) gavage. (B-C) An isoproterenol challenge test was conducted to assess the effects of olanzapine on isoproterenol-stimulated. Animals had *ad libitum* access to food and water. Baseline blood samples were collected and then isoproterenol (0.01 mg/kg) administered. Serial blood samples at 30-min intervals for 2h were collected to measure (B) FFA and (C) glycerol from isoproterenol-stimulated lipolysis. Data represent the mean ± S.E. (n = 8-10). Asterisks indicate significant differences compared to time-matched control values (*P<0.05, ***P<0.001). [Control = White Boxes, Olanzapine = Black Triangles]

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18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X_No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____ Yes
___X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding

period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Atypical antipsychotics rapidly and inappropriately switch peripheral fuel utilization to lipids, impairing metabolic flexibility in rodents.	Albaugh VL, Vary TC, Ilkayeva O, Wenner BR, Maresca KP, Joyal JL, Breazeale S, Elich TD, Lang CH, Lynch CJ:	Schizophr Bull	Jan 2012 (originally published May 2010)	☐Submitted ☐Accepted X Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____ No_____X_____

If yes, please describe your plans:

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its

impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

The ability of the metabolic side effect-prone- atypical antipsychotics to rapidly lower the Respiratory Exchange Ratio (RER) provides a rapid assay for this side effect. We have shown that those atypical antipsychotics that have reduced metabolic side effects do not possess this activity (1,2). Unfortunately, with compounds evaluated to date, there is a strong correlation between the efficacy of atypical antipsychotics for schizophrenia symptoms and the propensity to bring about metabolic side effects.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

The impact of our studies over time was to differentiate the hyperglycemia that atypical antipsychotics cause within minutes after they are ingested from the more traditional form of diabetes that develops over time in humans who take these drugs. In traditional diabetes, hyperglycemia occurs due to insulin resistance. Free fatty acids are utilized as an alternate fuel and these are replenished by adipose lipolysis which also increases lipolysis as a consequence. This provides a source of fuel. After olanzapine, lipolysis is impaired and lipogenesis in fat is increased. Since the drug at the same time increases fatty acid utilization and prevents glucose utilization, FFA levels drop and glucose accumulates in the serum. As we showed in later papers, at higher concentrations this is an unsustainable situation; when the doses are escalated, VO2 begins to decline. Over time the increase in the use of FFA as a fuel, probably increases the likelihood of conversion of obesity to obesity with diabetes due to lipotoxicity and increased oxidative stress. That is because FFA uses more oxygen than carbohydrate to oxidize which is the basis of the respiratory exchange ratio interpretations.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No_____X____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Christopher J. Lynch	Professor
eRA COMMONS USER NAME (credential, e.g., agency login)	
christopherlynch1	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Northeastern University, Boston, MA	B.S.	1978	Biology/Chemistry
Northeastern University, Boston, MA	Ph.D.	1984	Pharmacology
Howard Hughes Medical Institute & Dept of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, TN	Postdoc	1988	Physiology

A. PERSONAL STATEMENT.

Our laboratory is involved in obesity and metabolism research. One project focuses on the molecular signaling mechanisms of branched chain amino acids and their metabolism related to diet induced thermogenesis, insulin sensitivity and mTOR signaling. Recent collaborative contributions in this area include discovery of an energy wasting cycle in the BCATm KO mouse that stems from activation of protein turnover, molecular identity of the branched chain keto acid dehydrogenase phosphatase, establishing the quantitative importance of adipose tissue in BCAA metabolism and the mechanism of Leu and KIC mediated insulin release. Our focus on BCAA metabolism includes funded research on Maple Syrup Urine Disease. Another project seeks to understand the molecular mechanisms of the weight gain and metabolic side effects of atypical antipsychotics. This project involves human, animal and in vitro models. Other projects involve understanding the body weight independent effects of gastric bypass surgery and obesity-related drugs like topiramate and cannabinoids. I have been involved in the mentoring and research training of graduate, medical, undergraduate and post-docs and junior faculty for over 25 years including underrepresented minorities* (URM) and have been an NIH reviewer for URM training grant proposals. Trainees in **bold**.

B. POSITIONS AND HONORS.

Positions and Employment:

9/83-9/86 **Postdoctoral Research Fellow**, Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, TN 37232. (John Exton, MD PhD)

9/86-9/88 **Postdoctoral Research Associate**, Howard Hughes Medical Institute, Vanderbilt University School of Medicine, Nashville, TN 37232. (John Exton, MD PhD)

10/88-present **Professor, Associate Professor, Assistant Professor**, Department of Cellular and Molecular Physiology, College of Medicine and the Milton S. Hershey Medical Center, The Pennsylvania State University, 500 University Dr, Hershey, PA 17033.

8/04-present **Programmatic Area Leader**, Integrative Physiology of Diabetes and Obesity, Penn State Institute for Obesity and Diabetes

Awards & Professional Activities:

•1983-1986, PHS Individual National Research Service Award (AM 07274)
•1997-1999, Ciba-Geigy New Investigator Award •1990-1993, Editorial Board, American Journal of Physiology Endocrinology/ Metabolism
•1998, NIH Physiological Chemistry Study Section, ad hoc member
•1999, Topiramate in Obesity: Preclinical Scientific Review Group, member
•1997-99, American Heart Association, Cell Transport and Metabolism Study Section member
•1997-2000, Editorial Board, American Journal of Physiology Endocrinology/ Metabolism
•2001-03, American Physiological Society Endo-Met Steering Committee, member
•2001-03, American Physiological Society Endo-Met Secretary-Treasurer
•2003-05, American Physiological Society Membership Committee member
•2002, NIH Initial Review Group, ad hoc member: Metabolism Study Section
•2002, NIH Special Emphasis Panel, member: Diabetes and Vascular Function ZRG1
•2003-04, NIH Initial Review Group, ad hoc member: Metabolism Study Section
•2004, NIH Initial Review Group, ad hoc member: Cellular Aspects of Diabetes and Obesity (CADO)
•2004, U.K. Medical Research Council, Cancer and Cell Biology Program, Grant Reviewer
•2004, NIH ENMR Special Emphasis Panel, member
•2005, NIH Special Emphasis Panel, member: Molecular Aspects of Obesity and Diabetes
•2005, External Reviewer, Experimental Obesity Division, Pennington Biomedical Research Center (LSU, Baton Rouge, LA)
•2005, NIDDK Clinical Nutrition Research Units (CNRU) review panel, member
•2005-07, NIH Initial Review Group, regular member: Cellular Aspects of Diabetes and Obesity (CADO)
•2006, NIH Special Emphasis Panel, member: Pancreatic Beta Cell Development and Function (EMNR-BO2S)
•2008-09, NIH Initial Review Group, ad hoc member: Integrative Physiology of Obesity and Diabetes (IPOD)
•2008, NIA program project grant review panel, member
•2008-09, NIH CSR Special Emphasis Panels, member: ZRG1 ENMR-H-02G & Metabolic Endocrinology ZRG1 EMNR-H 02M; ZRG1 EMNR-B, ZRG1 EMNR-N (02) S, Diabetes, Obesity, and Endocrinology ZRG1 EMNR-B (02), and 2010/01ZRG1 DKUS C (30) Shared Instrumentation
•2010-2012, NIH, College of CSR Reviewers
•2010 NIH CSR Special Emphasis Panels, Chair: ZRG1 EMNR-B(03), Obesity and Cancer; member: ZRG1 EMNR-E (03) M Centers for Biomedical Computing; ZRG1 EMNR-C (55) Basic Translational Endocrinology, Metabolism and Digestive and Urological Systems; ZRG1 EMNR-D (02) M, Diabetes and Obesity, 2011/01 ZRG1 DKUS C (30) Shared Instrumentation
•2010 NIH CSR Special Emphasis Panel, Chair: ZRG1 EMNR-B(03), Obesity and Cancer
•2011 NIH Initial Review Group, Cellular Aspects of Diabetes and Obesity (CADO), Ad Hoc member
•2011 NIDDK: review panels for NIDDK Diabetes Research Centers, member; Mouse Metabolic Phenotyping Centers, Acting Chair
•2011 NIH CSR Special Emphasis Panels, member: ZRG1 EMNR-H (55) R - PAR-08-160: Metabolic Effects Psychotropic Medications, ZHD1-DR-K (10) Molecular Mechanisms of Adverse Metabolic Drug Effects, ZRG1 EMNR-D (55): Role of Environmental Chemical Exposures in the Development of Obesity, Type 2 Diabetes and Metabolic Syndrome.
2012 NIDDK Special Emphasis Panels: GRB-J M1, Professional Society Programs to Promote Diversity, member; ZDK1 GRB-S (O2) R, co-chair, ZDK1 GRB-S (O2) R NIDDK Diabetes Research Centers (P30), member,

•2012-13 NIH CSR Special Emphasis Panels: ZHD1-DR-K Metabolic Side Effects of Antipsychotics, member; NIH CSR Special Emphasis Panel, Reviewer Conflict Panel: 2014/01 ZRG1 EMNR-S (02) M, member

C. SELECTED PUBLICATIONS (from over 80)

1. Lynch CJ, Anthony J, **Patson BJ**, **Vaval A***, Jefferson LS and Vary TC. Leucine is a direct acting nutrient signal that regulates protein synthesis in adipose tissue. Am J Physiol Endocrinol Metab 2002; 283: E503-13.
2. **She P**, Reid T, Bronson, SK, Vary, TC, Lynch CJ* and Hutson SM. Disruption of BCATm in mice leads to increased energy expenditure associated with the activation of a futile protein turnover cycle. Cell Metabolism, 2007; 6; 181-94.(*corresponding author) PMCID: PMC2693888
3. **She P**, **Van Horn C,** Reid T, Hutson SM, Cooney RN and Lynch CJ. Obesity-related elevations in plasma leucine are associated with alterations in enzymes involved in branched chain amino acid (BCAA) metabolism. Am J Physiol Endocrinol Metab, 2007; 293: E1552-63. PMCID: PMC2767201
4. Lu, G, Sun, S, **She, P**, Youn, J-Y, Warburton, S, Ping, P, Vondriska, T, Cai, H, Lynch, CJ and Wang, Y. Protein Phosphatase 2Cm: A Key Regulator in Branched-Chain Amino Acid Catabolism. J Clin Invest 119: 1678-1687, 2009. PMCID: PMC2689111
5. **Culnan DM**, Cooney RN, Stanley B, Lynch CJ. Apolipoprotein A-IV, a putative satiety/antiatherogenic factor, rises after gastric bypass. Obesity (Silver Spring). 2009 Jan; 17(1):46-52. Epub 2008 Oct 23. PMCID: PMC2627784
6. **Meirelles K**, Ahmed T, **Culnan DM**, Lynch CJ, Lang CH, Cooney RN. Mechanisms of glucose homeostasis after Roux-en-Y gastric bypass surgery in the obese, insulin-resistant Zucker rat. Ann Surg. 2009 Feb; 249(2):277-85. PMCID: PMC2748974.
7. Herman, MA, **She, P**, Peroni, OD, Lynch, CJ, and Kahn, BB. Adipose tissue branched-chain amino acid (BCAA) metabolism modulates circulating BCAA levels. J Biol Chem. 285(15):11348-56, 2010. PMCID: PMC2857013.
8. **She P**, Zhou Y, Zhang Z, Griffin K, Gowda K, Lynch CJ. Disruption of BCAA Metabolism in Mice Impairs Exercise Metabolism and Endurance. J Appl Physiol. 2010 Feb 4. PMCID: PMC2853195.
9. **Albaugh VL**, **Judson JG***, She P, Lang CH, Maresca KP, Joyal JL, Lynch CJ. Olanzapine promotes fat accumulation in male rats by decreasing physical activity, repartitioning energy and increasing adipose tissue lipogenesis while impairing lipolysis. Mol Psychiatry. 2010 Mar 23. [Epub ahead of print] PMCID: PMC2892549.
10. Hajnal A, Kovacs P, Ahmed T, **Meirelles K**, Lynch CJ, Cooney RN: Gastric bypass surgery alters behavioral and neural taste functions for sweet taste in obese rats. Am J Physiol Gastrointest Liver Physiol 299:G967-979, 2010 PMCID: PMC2689111
11. **Albaugh VL,** Singareddy R, Mauger D, Lynch CJ. A double blind, placebo-controlled, randomized crossover study of the acute metabolic effects of olanzapine in healthy volunteers. PLoS One. 2011; 6(8):e22662. Epub 2011 Aug 9. PMCID: PMC3153475
12. **Albaugh VL**, Vary TC, Ilkayeva O, Wenner BR, Maresca KP, Joyal JL, Breazeale S, Elich TD, Lang CH, Lynch CJ. Atypical antipsychotics rapidly and inappropriately switch peripheral fuel utilization to lipids, impairing metabolic flexibility in rodents . Schizophr

Bull. 2012 Jan;38 (1):153-66. Epub 2010 May 21. PMCID: PMC3245588

13. **Klingerman CM, Stipanovic ME, Bader M**, Lynch CJ. Second-Generation Antipsychotics Cause a Rapid Switch to Fat Oxidation That Is Required for Survival in C57BL/6J Mice. Schizophr Bull. 2013 Jan 17. [Epub ahead of print] PMID: 23328157
14. **She P, Olson KC**, Kadota Y, Inukai A, Shimomura Y, Hoppel CL, Adams SH, Kawamata Y, Matsumoto H, Sakai R, Lang CH, Lynch CJ. Leucine and protein metabolism in obese Zucker rats. Anal Biochem. 2013 Aug 15;439(2):116-22. doi: 10.1016/j.ab.2013.05.002. Epub 2013 May 14. PMID 23684523, PMCID: In Progress
15. **Zimmerman HA, Olson KC**, Chen G, Lynch CJ. Adipose transplant for inborn errors of branched chain amino acid metabolism in mice. Mol Genet Metab. 2013 Aug;109(4):345-53. doi: 10.1016/j.ymgme.2013.05.010. Epub 2013 May 30.PMID: 23800641, PMCID: In Progress

D. RESEARCH SUPPORT

OTHER SUPPORT

Lynch, C.J.

ACTIVE

R01 DK084428-04 (Lynch, C.J.) 9/30/2010-6/30/2014
NIH $198,235 (DC Current Year)
"Mechanisms of Drug Side Effects Related to Obesity and Diabetes"
The long-term goals of this proposal are to elucidate the mechanisms of the metabolic side effects of atypical antipsychotics (e.g. olanzapine) that are used to treat psychiatric disorders like chizophrenia and other psychiatric disorders. We will develop an approach to rapidly predict the likelihood of obesity-related side effects in emerging compounds before they are tested in humans. This will aid in the design of next generation drugs with reduced side effects and may also reveal new therapeutic targets for the treatment of obesity and diabetes.
Lynch @ 25% effort
No overlap