

Weight Gain and Glycemic Regulation during Treatment with Olanzapine: Preclinical and Clinical Observations

Preliminary author list (in no particular order): A Breier, M Heiman, P Cavazzoni, M Sowell, CC Taylor, ...

Journal: *Biological Psychiatry* (?)

INTRODUCTION

1. Weight gain during treatment with antipsychotics in humans
 - a. Weight gain occurs during treatment with most antipsychotics (Stanton, 1995)
 - b. Appears to be greater during treatment with the atypical antipsychotic agents than typical agents (clozapine, risperidone, haloperidol) (Taylor, 2000; Allison, 1999; Wirshing, 1999)
 - c. The mechanism for antipsychotic drug-related weight gain is not known.
Possibilities include:
 - 1) improved mental state, eat better
 - 2) decreased level of activity, possibly due to sedation
 - 3) increased appetite
 - 4) metabolic and hormonal changes
 - 5) antagonism of neurotransmitters
 - a) dopamine
 - b) serotonin, especially 5HT_{2C}
 - c) histamine
 - d) catecholamines
 - 6) less akathisia with atypicals
 - d. Evidence suggests that weight gain during antipsychotic treatment is associated with the development of hyperglycemia or diabetes during treatment
 - 1) numerous case reports of development of hyperglycemia or diabetes during treatment with clozapine or olanzapine (Liebzeit, 2001)
 - 2) however, reports of increased risk of glucose dysfunction among patients with schizophrenia before introduction of antipsychotic agents
 - 3) further, in general population, not all obese people have diabetes and not all people with diabetes are obese
2. Weight gain during treatment with olanzapine
 - a. Approximately 2 to 4 kg above baseline during olanzapine treatment in clinical trials (6-28 weeks)
 - b. Categorical analyses of baseline to 1 year of olanzapine treatment indicated that approximately 24% of patients either have no weight gain or lose weight, 25% gain between 0 and 10 lbs., 39% gain between 10 and 30 lbs., and 12% gain more than 30 lbs.
 - c. In patients treated with olanzapine for up to 3 years, weight gain trended toward a plateau at approximately 39 weeks of treatment (Kinon et al, 2001)
 - d. Factors influencing olanzapine weight gain (Basson, in press, 2001):
 - 1) Underweight (perhaps overweight patients already have a higher body weight set point and can only be raised so much?)
 - 2) Better clinical outcome (degree of receptor occupancy?)
 - 3) Increased appetite

ZY 2196 1668

- a) *clinical reports that patients who have the greatest weight gain tend to report a markedly enhanced appetite soon after initiation of olanzapine, typically within the first few weeks*
 - b) *anecdotal reports indicate a food preference for carbohydrates although this has not been confirmed in controlled trials.*
- 3. Glycemic changes observed during treatment with olanzapine
 - a. Relatively small increases in mean random blood glucose levels during treatment for up to 52 weeks
 - b. Appears to be partially attributable to weight gain during treatment
- 4. Hypothalamic body weight set point
 - a. Human set point
 - 1) In adults, body weight is maintained at a relatively stable level for long periods of time; results from the coordinated activity of a complex system involving many components (Rosenbaum, 1997)
 - 2) Relatively low rates of energy expenditure and relatively high respiratory quotient (low fat to carbohydrate oxidation ratio) predict body weight gain; weight gain increases energy expenditure and fat oxidation that may oppose further weight change (Weyer, 2000)
 - 3) Set point theory – body weight is regulated at a predetermined level by a feedback control mechanism whereby information from the periphery is sent to the hypothalamus, information is integrated and transduced to modulate food intake or energy expenditure to correct any deviations in body weight from the set point (Harris, 1990)
 - 4) Maintenance of a reduced or elevated body weight is associated with compensatory changes in energy expenditure, which oppose the maintenance of a body weight that is different from the usual weight (Leibel, 1995)
 - 5) Chemical mediators of energy homeostasis:
 - a) *insulin*
 - b) *cholecystokinin (CCK)*
 - c) *leptin/leptin receptors*
 - d) *Neuropeptide Y (NPY)*
 - b. Rat set point
 - 1) *lesions of the ventromedial hypothalamus cause hyperinsulinemia, hyperphagia, and hypometabolism, resulting in obesity that is maintained by appropriate adjustments of food intake and energy expenditure, suggesting that lesions have altered a set point mechanism for regulating body weight (Harris, 1990)*
 - 2) *body weight regulation in the rat may involve both leptin and neurotensin (Sahu, 2001)*
 - 3) *no significant differences were found between the body weight set points of lipectomized and sham lipectomized rats, suggesting that the body weight set point is not mainly modulated by fat depots (Michel, 1998)*
- 5. Hypothesis: hypothalamic body weight set point is raised during treatment with antipsychotic agents
 - a. *Clinical observations (i.e., weight plateau)*
 - b. *We have attempted to test this hypothesis in rats*

ZY 2196 1669

PRECLINICAL STUDIES

Study 1 - Olanzapine vs. haloperidol or risperidone, rats with normal pancreatic function

1. Study 1 – Methods
2. Olanzapine vs. haloperidol and risperidone (0.1 and 0.3 mg/kg, s.c., for each drug) on food intake and lipid and carbohydrate metabolism (indirect calorimetry) in female Sprague-Dawley rats
 - a. Body composition, as measured by dual energy X-ray absorbometry before and after chronic (14 days) exposure to olanzapine
 - b. Effects of sibutramine (15 mg/kg)
2. Study 1 – Results
 - a. Haloperidol and risperidone stimulated FI and carbohydrate utilization (increase in respiratory quotient, RQ) but spared fat utilization.
 - b. Similar doses of olanzapine decreased FI and RQ but rats tended to be sedated
 - c. Without sedation, similar effects (Question: to haloperidol and risperidone? Was there some difference in fat utilization with olanzapine compared to haloperidol?) were observed during olanzapine treatment
 - d. Such adiposity and decreased lipid utilization was attenuated by sibutramine
3. Study 1 – Conclusions
 - a. Stimulation of adiposity may be observed during treatment with olanzapine, haloperidol, and risperidone.
 - b. Olanzapine, haloperidol, and risperidone may antagonize at least one neurotransmitter intimately involved in regulating energy balance at the hypothalamic level, which presents as hyperphagia and sparing of fat utilization (may act through different receptors/mechanisms)

Study 2 – olanzapine ad lib fed vs. olanzapine-treated (control) pair-fed and control, rats with normal pancreatic function

1. Study 2 - Methods
 - a. Olanzapine-treated (pamoate; 1 injection every 2 weeks; 160 mg/kg) vs. pair fed olanzapine-treated vs. control in female Sprague-Dawley rats
 - b. Assessments
 - 1) Body weight and food intake
 - 2) Body composition
 - 3) Plasma glucose
 - 4) Plasma insulin
 - 5) OGTT insulin
2. Study 2 - Results
 - a. Body weight and food intake
 - 1) In general, olanzapine-treated rats consumed more food, but quite variable
 - a) food intake leveled off after the second dose of olanzapine, toward end of the 14 d second and third dose period food intake picked back up
 - b) Does increased food consumption lead to transient changes in insulin levels that do not translate into longer-term abnormalities?
 - 2) Initially olanzapine-treated rats gained more weight, but control and pair fed groups caught up when weight gain with olanzapine began to level off over

ZY 2196 1670

- time and by end of the experiment the weight of the olanzapine-treated rats was pretty close to controls
- 3) The rate of weight gain was greater with olanzapine after the first injection and similar between the three groups after the second and third injections
 - a) approaching set point or sedation from second injection raising levels? weight gain didn't appear to be slowing down as approached 14 d time point
 - b) if drug raised set point it didn't sustain increased set point, OR sedating animals, OR OTHER?
 - 4) Throughout, pair fed olanzapine-treated rats had weight gain similar to control group, suggesting that olanzapine-treated group gained more weight because they consumed more food
 - 5) Therefore, olanzapine may be interfering with the hypothalamic set point that regulates food intake (via histamine, dopamine, 5HT_{2C} receptor antagonism, and possibly regulated by leptin)
- b. Body composition
- 1) Following 49 days, control rats had more lean mass compared to fat mass than olanzapine-treated rats
 - 2) Olanzapine-treated rats are increasing their fat composition because of increased food intake (fat-sparing; take in more carbs, burn more carbs)
 - 3) Of the three groups, the pair fed olanzapine-treated rats had the most fat mass compared to lean mass (Question: Do weight control measures such as nizatidine, amantadine, or sibutramine generate similar end result [i.e., less net weight gain cause you to eat less but more total body fat]?).
 - 4) Pair fed rats have the same food intake as control rats but act like starving (lean mass is being utilized) because set point has increased
- c. Plasma glucose
- 1) Plasma glucose not different between olanzapine-treated, pair fed, and control (and by end of the experiment neither are insulin levels, but weight difference at this point not impressively different between olanzapine-treated and control group [$< 5\%$])
 - 2) With increased load of food, compensatory increase in insulin levels to maintain plasma glucose levels
- d. Plasma insulin
- 1) In all groups, increased insulin early on during "feeding frenzy" (don't know if statistically significant) but glucose not really different (more food intake, more insulin, then levels off)
 - a) cause of or response to the overfeeding?
 - b) appear to be somewhat insulin resistant
 - c) once rate of weight gain slows the insulin levels start coming down (cause or response?)
 - 2) Olanzapine-treated animals did not have elevated insulin (perhaps a little lower); therefore, hyperinsulinemia does not appear to be causing feeding and, in absence of over-eating, olanzapine-treated animals don't get higher insulin levels

ZY 2196 1671

- 3) Might expect to see increased insulin levels as recalibrating to new set point (as result of overfeeding); once there, might level out but this depends a lot on whether there is other baggage, such as the increased fat mass accumulated as a result of reaching this new set point
 - 4) At the end of the experiment, the 3 groups were not different (difficult to determine if earlier points are significant [only have 4-5 animals?])
- e. OGTT insulin
- 1) No difference between the three group at the end of the experiment when everything seems to have normalized between the 3 groups
 - 2) The AUC for insulin in olanzapine pair fed looks larger than others, but the glucose AUC is LOWER in this group of animals (not pattern for insulin resistance, where one would expect glucose to be the same with higher insulin [Note: need to see glucose curves for the OGTT experiments])
 - 3) Possible explanation: increased fat composition, increased glucose uptake by adipocytes, therefore increased insulin and lower glucose
3. Study 2 – Conclusions
- a. No direct (permanent negative) effect of olanzapine on the pancreas, but increased hypothalamic body weight set point
 - b. Weight gain with olanzapine plateaus over time (To get at mechanism, should look at plasma drug levels during these studies. What would happen if you just gave single dose and followed past 14 days? Would the elevated rate of weight increase continue, and, if so, for how long? Since end up at same final weight, is “set point” same for control and olanzapine-treated at the end of the experiment)

Study 3 - olanzapine ad lib fed vs. olanzapine-treated (control) pair-fed and control, rats with abnormal pancreatic function (Note: These data are uninterpretable in current form, see additional studies needed below)

1. Study 3 - Methods

- a. ZDF rat – weak pancreas, with certain diet pancreas will fail at 8 weeks, therefore give treatment at 6 weeks to see if it will be driven to diabetes
- b. Assessments
 - 1) Body weight and food intake
 - 2) Plasma glucose
 - 3) Plasma insulin

2. Study 3 – Results

- a. Body weight and food intake
 - 1) Control rats consume more than olanzapine-treated and pair fed (Did olanzapine-treated not eat because in ZDF's higher drug levels attained and animals sedated? Or in a leptin deficiency background, olanzapine acts as weight loss agent?)
 - 2) All gained weight over time, but no difference between groups
 - 3) Pair fed group has increased rate of weight gain at approx. week 38, which crosses over olanzapine-treated group (possible explanation?)
- b. Plasma glucose
 - 1) Over time (35 days), parallel rise then leveling off at high level with all groups (argues against the possibility that the lesser weight gain of

ZY 2196 1672

- olanzapine-treated group is due to relatively decreased food intake because of sedation [i.e., if eating less would expect to see relatively decreased glucose])
- 2) Control > olanzapine > pair fed
- c. Plasma insulin
- 1) Parallel pattern over time, initial increase then decrease, with olanzapine and pair fed reaching a higher level than control (for olanzapine pair fed, in order to have a compensatory increase in insulin, must have enough food intake)
 - 2) Insulin levels rise more slowly (delayed response because of lower initial glucose levels?)
3. Study 3 – Conclusions
- a. At first they try to compensate for increased glucose with increased insulin, then the pancreas gives up
 - b. Pancreatic failure did not occur any earlier with olanzapine treatment than control, suggesting no direct effect on the pancreas
 - c. Additional studies are needed
 - 1) control untreated animals where food intake is matched to the olanzapine group.
 - 2) assess sedation and drug levels

DISCUSSION

1. Overall conclusions
 - a. At least in the rat, no direct (permanent negative) effect of olanzapine on the pancreas, but increased hypothalamic body weight set point and weight gain plateau (don't know if plateau was real or artifact of above mentioned possible confounders)
 - b. Olanzapine-treated rats are gaining weight (increased fat) but may be metabolically different fat, therefore possibly less risk of diabetes (i.e., once get to new set point, less at risk?)
 - 1) Further analysis needed (earlier time point [?] when discrepancy between control and olanzapine-treated [OGTT at these time points, or, better yet, clamps]; the olanzapine pair fed at end have more total body fat and don't look too bad from fasting insulin and glucose standpoint but the OGTT data is questionable)
 - c. Antipsychotics may antagonize at least one neurotransmitter intimately involved in regulating energy balance at the hypothalamic level, which presents as hyperphagia and sparing of fat utilization
 - 1) olanzapine pharmacology with regard to what is known about neurotransmitter receptor regulation of body weight
 - a) in rodents, serotonin inhibits the ingestion of carbohydrate, more than fat or protein (Leibowitz, 1998)
2. How does the rodent data compare with human data and what has been observed in olanzapine clinical trials?
 - a. Similarities
 - 1) Overweight don't gain as much weight as underweight (set point is already high) (ZDF data?)
 - 2) Some weight loss in overweight individuals (ZDF data?)

ZY 2196 1673

- 3) Weight gain reaches a plateau over time (However, olanzapine-treated patients at plateau are significantly heavier than patients not receiving olanzapine, so difference between the two groups does not narrow [the "control" group is not gaining substantial weight in the human experiment])
- b. Differences
 - 1) No effect of olanzapine on plasma glucose levels in rodent studies
 - a) however, FASTING glucose concentrations in animals
 - b) available human data (Korea stat report), so far no change in fasting glucose concentrations (in contrast to random glucose increase of approximately 4 mg/dl in the clinical trial database)
3. Future research

ZY 2196 1674