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Metabolic impairments precede changes in hunger and food intake following short-term administration of second generation antipsychotics

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Introduction

The second generation antipsychotics (SGA) developed to treat schizophrenia, are associated with weight gain (1;2) and metabolic disease (3;4). Short- term administration has been shown to increase indices of metabolic impairment (fasting glucose, insulin and triglycerides) (5;6) while chronic SGA treatment increases the incidence of diabetes (7;8) and cardiovascular disease (9). Of concern is the observation that the most therapeutically effective agents are associated with the most severe adverse metabolic profiles. Olanzapine, a drug widely prescribed for schizophrenia and bipolar disorder in adults and children is associated with significant weight gain and metabolic abnormalities (1;10). Other SGAs, such as aripiprazole are thought to be associated with modest weight gain and fewer indices of metabolic disease (11).

The observed metabolic dysregulation is assumed a downstream effect of increased body weight due to SGA-associated changes in the central nervous system mechanisms regulating food intake and energy homeostasis. In vitro (12;13) and rodent studies (14;15) suggest that the SGAs may exert direct effects on tissue function independent of weight gain, raising questions as to whether metabolic dysregulation is solely a consequence of increased body adiposity. Our laboratory has recently demonstrated that short-term administration of SGAs alters metabolism, independent of weight gain. We administered olanzapine, aripiprazole or placebo to healthy control subjects (10 subjects in each interventional arm) for a 9-day period and conducted metabolic tests evaluating insulin sensitivity and hormonal secretion

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to a mixed nutrient challenge, prior to and following the interventions. Uniquely, this was an inpatient study in which subjects were permitted to eat ad libitum but were required to maintain their activity level in the hospital consistent with their free living level. We were able to demonstrate that both olanzapine and aripiprazole induce insulin resistance but only olanzapine elicits post-prandial metabolic dysregulation. These effects were shown to be independent of weight gain or changes in food intake (16).

Few studies have investigated detailed eating behaviors initially after drug administration and it is not known how and when the SGAs influence food intake, hunger and satiety during the early time period after starting treatment. This current paper presents the detailed results of the effect of two SGAs compared to placebo on eating behaviors and associations between food intake and weight variation which were not reported in the original paper. The study was approved by the Institutional Review Board of the University of Pennsylvania and all subjects gave their written informed consent.

Methods

For a detailed description of design, methodology and metabolic results see our earlier report (16). Methods for evaluation of hunger, fullness and food intake are explained here. Visual analog scales for ratings of hunger and fullness were completed daily immediately before and following each meal. The questions were phrased: “how hungry do you feel right now?” and “how full do you feel right now?” Each question had the numbers 1–9 listed underneath anchored by the descriptors, “not at all” and “extremely”.

Subjects were permitted to eat ad libitum while in the hospital. Meals were selected from a menu and the food was prepared in the metabolic kitchen of the Clinical and Translational Research Center (CTRC). On days 2 (pre- intervention) and 11 (post-intervention) of the 12-day inpatient stay, at each meal, subjects were given a menu composed of individual food items so that macronutrient composition could be accurately determined as previously described (17). Selected foods were provided in excess of normal portions but unknown to the subjects all food was weighed prior to and following breakfast, lunch, dinner and snack.

Results

As initially reported in our original paper, following the short-term administration of olanzapine, aripiprazole or placebo, change in weight after 9-days of olanzapine (0.76±0.42 kg) or aripiprazole (−0.46±0.31 kg) was not significantly different from the change after placebo (0.41±0.34 kg). Activity as indicated by the number of steps taken while in the 12-day study was not significantly different than the average taken over 5 days in a free living condition indicating that activity levels were maintained. No significant difference was found in the pre-post change in step number while on olanzapine (−910.5±636.36), or aripiprazole (−547.7±258.7) compared with the change in placebo (−334.2±234). The change in kcals ingested after olanzapine (363±380.6 kcal, t=0.39, P=0.70) or aripiprazole (−269.9±552.6 kcal, t=−0.64, P=0.53) was not different from placebo (162.1±339.7 kcal). Consistent with a lack of change in weight or food intake, we did not find any effect of olanzapine (Fig. 1a) or aripiprazole (Fig. 1b) compared to placebo (Fig. 1c) on subjective

feelings of hunger, whether analyzed using repeated measures analysis of variance or total hunger over the 12 day period (Fig. 1d). Similarly, no effect of fullness was observed (Fig. 1e, f, g, h).

The orexigenic hormone ghrelin and the satiety hormone leptin responses to the meal challenge were measured in a sub-group of participants from the larger study prior to and following the interventions. No significant differences were found in the change in ghrelin AUC after either olanzapine (−956.0±422.2 pg/ml/360 min, t=0.26, P=0.79) or aripiprazole (−856.4±458.4 pg/ml/360 min, t=0.4, P=0.69) when compared to placebo (−1118.7±445.0 pg/ml/360 min) (Fig. 2d). Similarly no change in post-prandial leptin AUC after olanzapine (13.5±7.8 ng/ml/360 min, t=0.49, P=0.63,) or aripiprazole (−4.1±2.9 ng/ml/360 min, t=1.3, P=0.21) compared to placebo (7.5±8.9 ng/ml/360 min, Fig. 2h)

Discussion

The objective of this paper was to evaluate the acute effects of two SGAs on food intake and hunger in an inpatient setting where activity was controlled. We found no changes in subjective feelings of hunger or satiety, food intake or the appetite-related hormones leptin and ghrelin during 9 day inpatient administration of olanzapine or aripiprazole compared to placebo. The lack of change in hunger and food intake is consistent with the absence of weight gain despite drug-induced changes in post-prandial hormones and decreases in insulin sensitivity as we previously reported (16). The data presented here document the lack of an early change in eating behavior after SGA administration and suggest that in the initial period after SGA administration, the mechanisms mediating the metabolic impairments are independent of changes in food intake, and so would be expected to precede and possibly even contribute to any eventual changes in body weight.

A typical sequence of eating behavior under “real-life” circumstances would involve an increase in hunger precipitating an increase in food intake. Sustained increases in food intake in the absence of satiating mechanisms result in weight gain. While the effects of SGAs on weight gain, particularly olanzapine, are indisputable, documentation of increases in hunger is notably absent. Only two studies have measured hunger after olanzapine administration to healthy volunteers and neither found statistically significant increases (18;19). We measured hunger and fullness multiple times per day over the entire 12-day period and similarly, did not find any effect of either olanzapine or aripiprazole on feelings of hunger. Ghrelin, the only circulating hormone known to be associated with hunger (20) was unaffected by the interventions and was not correlated with hunger, food intake (data not shown) or change in weight .

Under our experimental conditions, we found no significant decreases in satiety as indicated by fullness ratings which remained equal across the three study conditions (Fig. 1). Both insulin and leptin are considered satiety hormones and theoretically contribute to long-term energy homeostasis in insulin sensitive individuals (22). The rapid onset of olanzapine-induced post-prandial hyperinsulinemia that we previously reported may have implications with regards to promoting weight gain through the anabolic actions of insulin and at the same time, initially contributing to satiety prior to induction of central insulin resistance

(23). This could perhaps explain the lack of decrease in satiety during the early period of time after SGA administration. The effects of olanzapine on decreasing satiety and ultimately increasing food intake may only occur following an increase in body adiposity which is thought to lead to central insulin and leptin resistance.

Short-term administration of the SGAs to healthy volunteers has, in some studies, elicited small increases in body weight (18;19;21;24;25) but food intake itself has rarely been monitored. Only three studies monitored (18;19;21) both food intake and body weight. While increases in body weight were reported with all 3 studies (18;19;21), only one found a statistically significant increase in food intake but the measurement was based on consumption of a liquid breakfast in the absence of placebo control (19). In contrast to these studies, we conducted an inpatient study where activity was maintained constant to pre-study level. Consistent with the absence of weight gain, we found no differences in total food intake following administration of either SGA compared to placebo. However, we did find highly statistically significant correlations between an index of total food intake (sum of food consumed on pre- and post-intervention days) and change in weight for the group as a whole ($R=0.55$, $P<0.002$), placebo ($R=0.83$, $P<0.001$), and olanzapine ($R=0.63$, $P<0.01$). Only aripiprazole was not associated with a correlation between change in weight and the index of total food intake.

Overall the data presented here, as well as in our earlier publication(16), indicate that under conditions where activity is controlled, the SGAs olanzapine and aripiprazole are associated with metabolic changes in healthy subjects that occur prior to changes in hunger, satiety, food intake and appetite related hormones and in the absence of weight gain. The temporal separation of the metabolic disturbances and behavioral effects suggests that there are differential mechanisms mediating SGA induced changes in metabolism and food intake, which may be a later consequence to subsequent changes in body weight. However, one limitation that must be acknowledged is the possibility that clinical populations may respond differently than this healthy control group.

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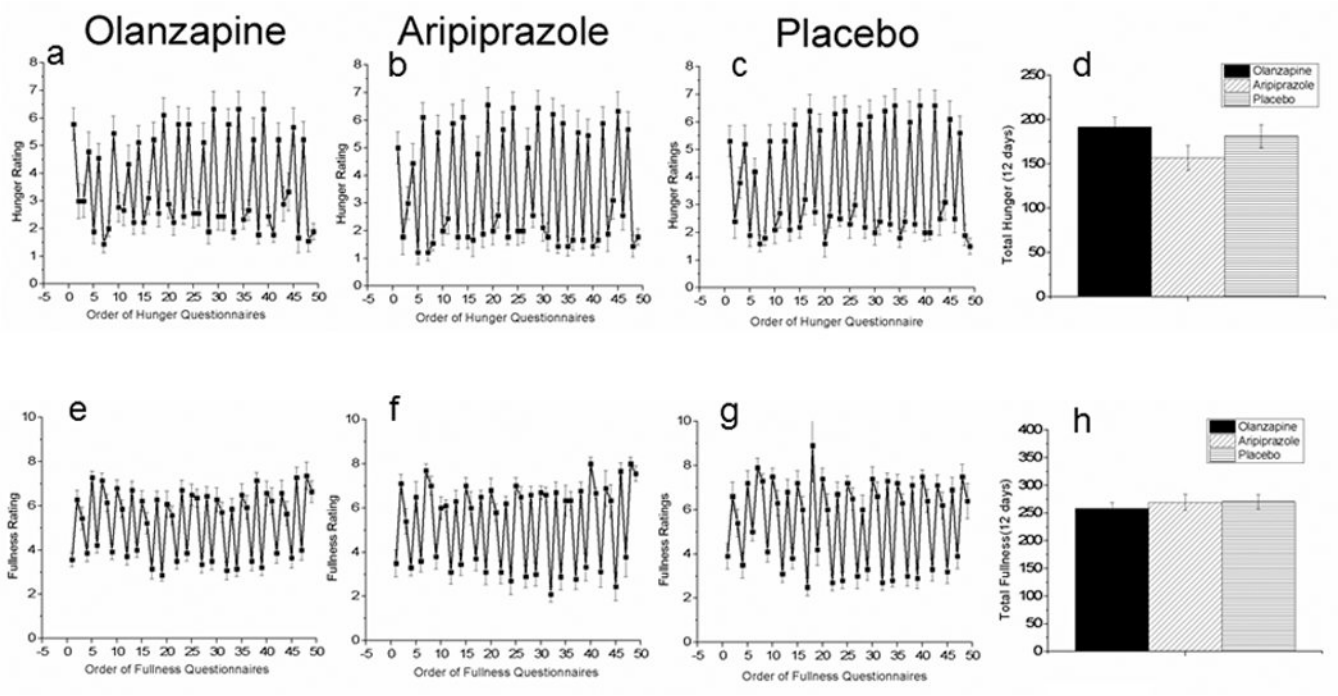

Figure 1.

Hunger ratings during administration of olanzapine (a), aripiprazole (b) and placebo (c) over the course of the 12-day inpatient study. Fig. 1d illustrates the total hunger score over the 12-day period: daily fullness ratings during administration of olanzapine (e), aripiprazole (f) and placebo (g) over the course of the 12-day inpatient study. Fig. 1h illustrates the total fullness score over the 12-day period. Mean±S.E., n=10; olanzapine; n=10 aripiprazole: n=10 placebo.

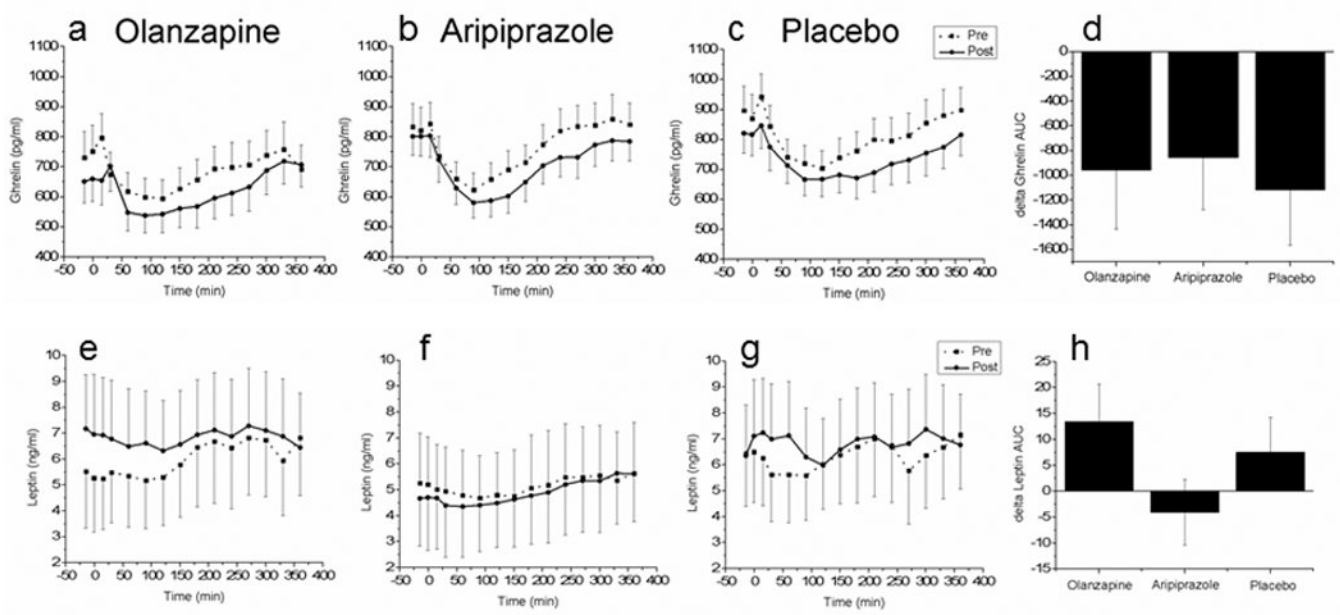

Figure 2.

Post-prandial plasma ghrelin concentrations prior to (dashed line) and after (solid line) administration of olanzapine (a), aripiprazole (b) and placebo (c). Fig 3d illustrates the delta area under the curve (AUC) (post-intervention AUC- pre-intervention AUC). Post-prandial plasma leptin concentrations prior to (dashed line) and after (solid line) administration of olanzapine (a), aripiprazole (b) and placebo (c). Fig 3h illustrates the delta area under the curve (AUC) (post-intervention AUC- pre-intervention AUC). Mean±S. E., for leptin n=7, 9, 8 and ghrelin, n= 6,5,7 for olanzapine, aripiprazole and placebo, respectively.