Proceedings of the Nutrition Society (2008), **67 (OCE)**, E204 doi:10.1017/S0029665108008367

Joint meeting of the Société Française de Nutrition and The Nutrition Society, 6–7 December 2007

Disturbances in energy metabolism induced by antipsychotic treatments in a rat model

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New antipsychotic drugs (termed 'atypical') induce metabolic disturbances resembling those of the metabolic syndrome, i.e. excessive weight gain, impaired glucose homeostasis and hypertriacylglycerolaemia in both genders(1). However, the mechanisms by which antipsychotics induce these undesirable side effects in human subjects are not known, and require investigation in animal models. In the rat atypical antipsychotic drugs were thought to increase body weight in females only, until a model of antipsychotic-induced weight gain in male rats was developed(2). This model was used to study the effects of chronic administration of two antipsychotic drugs *v*. a control group (six rats per group): haloperidol (1 mg/kg diet), a classical antipsychotic drug inducing a moderate weight gain in human subjects; olanzapine (2 mg/kg diet), an atypical antipsychotic drug with a greater effect. Rats were given a Western-type diet (% energy; 14 as protein, 31 as lipid, 54 as carbohydrate) and the drugs were provided in the food for 6 weeks. Food intake and body weight were measured twice weekly. After 4 weeks an oral glucose tolerance test (0.2 g glucose/100 g body weight) was performed in fasted rats. Blood samples were obtained before and 10, 30, 60 and 120 min after the glucose load for the determination of glucose and insulin concentration. After 6 weeks body composition was measured. Blood glucose and plasma insulin, TAG, total cholesterol and HDL-cholesterol concentrations were also assayed.

Haloperidol-treated rats did not differ from control rats for any variable throughout the experiment. After 4 weeks fasting glycaemia was significantly higher in olanzapine-treated rats (0.87 g/l) than in the control group (0.75 g/l), and increased more rapidly after the glucose load (1.22 g/l *v*. 0.97 g/l after 10 min). By contrast, the insulin curves were similar for the olanzapine-treated and control groups. After 6 weeks fasting glycaemia remained higher in olanzapine-treated rats (1.46 g/l *v*. 1.25 g/l for control rats). Although there were no differences in body weight, body-weight gain or food intake, the percentage epididymal adipose tissue was significantly higher in olanzapine-treated rats (1.63) than in control rats (1.44). Other plasma variables did not differ significantly.

In conclusion, male rats treated with an atypical antipsychotic drug show an early disturbance in energy metabolism that is associated with impaired glycaemic regulation and visceral obesity without an increase in food intake. This model can be used to explore the mechanisms of antipsychotic drug-induced metabolic syndrome, and the possibility of nutritional support.

1. American Diabetes Association (2004) *Diabetes Care* **27**, 596–601.
2. Minet-Ringuet J, Even PC, Lacroix M, Tome D & de Beaurepaire R (2006) *Psychopharmacology* **187**, 447–454.