MECHANISTIC CONNECTIONS BETWEEN GLUCOSE/LIPID DISTURBANCES AND WEIGHT GAIN INDUCED BY ANTIPSYCHOTIC DRUGS

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Antipsychotic drugs produce an array of metabolic side effects including elevated serum lipids (especially triglycerides), hyperglycemia, significant weight gain and even diabetes in some patients. This review will focus on possible molecular mechanisms by which the drugs affect metabolic function. There appears to be a connection between the drug-induced lipid and glucose disturbances and weight gain in patients. The relationship between these metabolic effects stems from operation of the glucose-fatty acid cycle and the cooperative regulation of energy metabolism at the level of signaling pathways, including Akt and AMPK, which converge on forkhead and C/EBP transcription factors. Genetic studies have provided some insight into the possible pharmacological basis for drug-induced weight gain with apparent contributions by histamine H1 and serotonergic (5-HT2C) receptors. However, additional targets of the drugs must be involved in the induction of the metabolic syndrome. These targets may include

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glucose transporters, cytochrome P450 enzymes, aryl hydrocarbon receptors, K^+ channels, and glucose-sensing systems in general. Additional clues have emerged from animal models. Antipsychotic drugs produce hyperglycemia and weight gain in mice and rats. Moreover, the drugs stimulate lipid accumulation in the nematode, *Caenorhaditis elegans*, a valuable genetic tool for elucidation of molecular targets involved in diverse biological responses. A better understanding of the drug-induced side effects may ultimately allow identification of risk factors in patients and prevention of weight gain and glucose disturbances with adjunctive approaches. Finally, knowledge of the molecular basis of these emergent syndromes may inspire the development of the next generation of antipsychotic drugs with minimal metabolic liability.

I. Introduction

Over the past 10 years, there has been a growing appreciation of the adverse metabolic effects produced in patients by the second-generation antipsychotic drugs (Allison *et al.*, 1999; Baptista *et al.*, 2002; Dwyer *et al.*, 2001; Henderson *et al.*, 2000; Haupt and Newcomer, 2001; Lindenmayer *et al.*, 2003; Wetterling and Muessigbrodt, 1999; Wirshing *et al.*, 2002). The clinical importance of these metabolic side effects was highlighted in the recent decision (in 2003) by the Food and Drug Administration (FDA, to require warning labels on second-generation drugs concerning the possibility of drug-induced diabetes, including diabetic ketoacidosis. This move was followed in 2004 by joint recommendations formulated by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity for monitoring weight gain, glucose intolerance, and hypertension in patients treated with second-generation antipsychotics (American Diabetes Association, Consensus Statement, 2004). However, the adverse metabolic effects of antipsychotics are by no means limited to the newer second-generation drugs. Disturbances in glucose regulation and weight gain were noted for some of the older drugs, especially chlorpromazine and loxapine (Arneson, 1964; Hiles, 1956; Kalucy, 1980; Tollefson and Lesar, 1983). With the conventional antipsychotics, the focus was instead on drug-induced movement disorders—the extrapyramidal symptoms, including tardive dyskinesia (Faurbye, 1970). The clinical implications of the metabolic disturbances associated with antipsychotic treatment are discussed in some detail in this chapter and are the main subject of recent excellent reviews (Baptista *et al.*, 2002; Casey, 2004; Newcomer, 2004; Wirshing, 2004).

It has been known for some time that various drugs induce weight gain and even diabetes in patients. In general, the connection between weight gain and the second-generation antipsychotics is well accepted. However, the role of these drugs in the induction of diabetes is more controversial. There are older reports of an increased incidence of diabetes in schizophrenic patients compared to the general population (Simon and Garvey, 1951; Waitzkin, 1966), and relative insulin resistance among psychotic patients was observed during trials of insulin shock therapy for psychosis prior to the introduction of antipsychotic drugs (Sakel, 1938). Irrespective of the baseline risk of diabetes in schizophrenia, case reports describe patients who developed hyperglycemia shortly after the start of antipsychotic drug treatment and resolution of the hyperglycemia on discontinuation of drug; reappearance of elevated glucose levels has also been observed with reinstitution of drug (Koller and Doraiswamy, 2002; Koller *et al.*, 2001; McIntyre *et al.*, 2001). In further support of the contribution of drugs to emerging glucose dysregulation, Arranz *et al.* (2004) recently reported normal glucose metabolic parameters in antipsychotic-naive patients in comparison to controls, whereas previously-medicated patients exhibited a significant increase in insulin resistance. The mechanisms involved in the drug-induced metabolic effects of antipsychotic drugs are still unknown. Therefore, our goal is to provide a thorough analysis of possible mechanisms of action that might contribute to the metabolic disturbances in patients. It is our general thesis that the metabolic side effects are not adequately explained by the established pharmacology of the antipsychotic drugs; additional mechanisms must be involved. Moreover, we explore the possibility of mechanistic connections between drug-induced glucose and lipid disturbances that frequently emerge as diabetes or weight gain depending on patient susceptibility. We believe it is unlikely that glucose and lipid disturbances, including weight gain, are brought about through separate, unrelated pathways. Furthermore, many other drug classes are noted for their ability to induce glucose abnormalities and weight gain. Each drug class could produce these metabolic effects via unique pathways; however, we favor the possibility that common mechanisms are involved.

Regrettably, we are unable to cite all of the literature related to the topic of this chapter. Of necessity, our focus is somewhat restricted; therefore readers are referred to recent reviews for additional references and in-depth discussion (Baptista *et al.*, 2002; Casey, 2004; Newcomer, 2004; Wirshing, 2004).

II. Metabolic Effects: Glucose Disturbances and Diabetes

The incidence of diabetes in the general population is currently estimated to be about 5–6% (International Diabetes Federation Consensus Workshop, 2004; Diabetes in Children and Adolescents Work Group, 2004). By contrast, various

groups have reported that the incidence of diabetes in schizophrenic patients treated with antipsychotic drugs is in the range of 10–35% (Baptista *et al.*, 2002; Hagg *et al.*,1998; Henderson *et al.*, 2000). Additional patients may have impaired glucose regulation without frank diabetes. If we accept the idea that the drugs produce glucose abnormalities in at least a subset of patients, the question then becomes how do the drugs interfere with normal glucose regulation? From a theoretical perspective, normal glucose metabolism could be adversely affected by antipsychotic drugs via (1) a decrease in insulin production, (2) reduced insulin sensitivity, (3) alterations in other glucoregulatory hormones and factors, (4) altered energy metabolism (i.e., a reduction in glucose utilization), (5) increased gluconeogenesis, and (6) defective glucose sensing. In relation to points 1 and 2, there is little evidence to support a decrease in insulin secretion as the major factor involved in drug-induced hyperglycemia (Sowell *et al.*, 2002). In fact, most studies report hyperinsulinemia (Melkersson *et al.*, 2000; Newcomer *et al.*, 2002; Yazici *et al.*, 1998), and studies of insulin sensitivity in patients have revealed conflicting findings. Newcomer *et al.* (2002) and Henderson and Ettinger (2002) reported a decrease in insulin sensitivity in patients treated with second-generation antipsychotic drugs, whereas Sowell *et al.* (2002) found no significant change in the insulin response of normal subjects treated acutely with olanzapine and risperidone. Differences in the treatment conditions (chronic vs. acute) and study populations (patients vs. normal volunteers) may explain the discrepancies in these studies. Of course, the drugs may also induce a combination of deficits to produce diabetes such as a reduction in insulin sensitivity concomitant with an increase in gluconeogenesis. Regardless of the precise path toward a disturbance in glucose regulation, these processes outlined lie downstream of the ultimate target of the antipsychotic drugs. Some of the likely targets are considered here.

A. Direct Effect of Drugs on Glucose Transport

Previously we showed that high concentrations of certain antipsychotic drugs inhibited glucose transport into neuronal cells and other cell types (Ardizzone *et al.*, 2001; Dwyer *et al.*, 1999a,b). The drugs were noncompetitive inhibitors of transport and competed with cytochalasin B (a selective inhibitor and photoaffinity label for the glucose transporter [GLUT]) for binding to the GLUT protein (Ardizzone and Dwyer, 2002; Dwyer *et al.*, 2002). We speculated that interference with glucose transport may, at some level, contribute to the observed hyperglycemia in patients. The effects of antipsychotic drugs on glucose transport have recently been reviewed in an earlier volume of this series (Dwyer *et al.*, 2002); readers are referred there for a more detailed account of these findings. In addition to these *in vitro* studies, we showed that administration of antipsychotic

drugs to mice induced acute hyperglycemia in relation to the effects of the drugs on glucose transport (Dwyer and Donohoe, 2003), that is, drugs that potently inhibited glucose transport *in vitro* produced the highest blood glucose concentrations in mice. Nevertheless, there are certain limitations in extrapolating from the *in vitro* data. The concentrations of drug that block glucose transport in cell lines (2–40 μM) are higher than serum concentrations under steady-state conditions in patients, which are in the range of 0.02–1 μM depending on the drug (Olesen, 1998; Olesen and Linnet, 1999; Robertson and McMullin, 2000 Ulrich *et al.*, 1998). Furthermore, inhibition of glucose transport by the antipsychotics is diminished in high glucose conditions, suggesting that under normal circumstances the drugs may produce limited interference with glucose transport in many tissues.

Several findings support the possibility that interference with glucose transport by the antipsychotic drugs may contribute to the metabolic effects in patients with normal dosing. First, antipsychotic drugs are accumulated 25- to 30-fold in tissues such as fat and brain (Aravagiri *et al.*, 1995; Baldessarini *et al.*, 1993; Cohen *et al.*, 1992; Kornhuber *et al.*, 1999; Weigmann *et al.*, 1999), which means that ambient concentrations may reach the levels needed to affect glucose transport. Second, certain metabolites of the antipsychotic drugs are far more potent than the parent compound at inhibiting glucose transport (Ardizzone *et al.*, 2001). Thus, the concentrations and nature of drug metabolites may be significant factors. Third, clozapine at clinically relevant doses produced significant hyperglycemia in mice (Dwyer and Donohoe, 2003). Cytochalasin B at the same dose as clozapine induced comparable hyperglycemia and the only known relevant action of this compound is to inhibit glucose transport by direct blockade of GLUTs (Dwyer and Donohoe, 2003; Dwyer *et al.*, 2002). Therefore, direct actions of the drugs on glucose transport cannot be ruled out as a contributing factor to the emergence of hyperglycemia in patients.

B. Interference with Glucose Sensing

Various cells in the body have evolved as specialized sensors of glucose concentrations that respond by regulating aspects of glucose metabolism. In particular, cells in the pancreas, gut, and brain monitor glucose and mount responses when glucose levels rise or fall beyond certain thresholds. These cells control the secretion of insulin, gut hormones (including incretins), and regulate feeding and adaptive responses (Schuit *et al.*, 2001). The glucose-sensing mechanisms are best understood in β cells of the pancreas and hypothalamic neurons in the brain (Efrat *et al.*, 1994; Levin *et al.*, 2002; Matschinsky and Collins, 1997). At a minimum, the sensor is composed of glucokinase, which phosphorylates incoming glucose; the high-Km transporter, GLUT2; and adenosine triphosphate

(ATP)/sulfonylurea–sensitive K^+ channels (Bell *et al.*, 1996; Efrat *et al.*, 1994; Matschinsky and Collins, 1997). This system appears to have largely evolved to govern the secretion of insulin by cells and neurotransmitter in glucose-sensing neurons.

Interference with glucose sensing, directly or indirectly, has a significant impact on energy metabolism in man. For example, inhibition of glucose transport in glucose-sensing cells by an antipsychotic drug would falsely lead those cells to perceive a state of glucose deprivation. Consequently, the systems regulated by those cells may respond by decreasing glucose utilization, stimulating glycogen breakdown and perhaps gluconeogenesis, altering lipid metabolism, and mobilizing alternative fuel supplies. The end result would be an acute hyperglycemic response with the emergence of glucose intolerance in susceptible individuals over time. Similarly, if an antipsychotic drug reduced the efficiency of glucose utilization in glucose-sensing cells via direct mitochondrial effects, these cells may incorrectly perceive a shortfall in available energy and stimulate mobilization of glucose reserves and production. Again, hyperglycemia might result because there are actually normal levels of glucose in circulation, and glycogen breakdown and gluconeogenesis would add yet more glucose to the system. Finally, the antipsychotic drugs may interfere with other signaling in the glucose-sensing pathway. It is known that clozapine and other antipsychotics inhibit K^+ channels (Kobayashi *et al.*, 2000; Muller *et al.*, 1991; Wu *et al.*, 2000). Perhaps the drugs that cause hyperglycemia in patients inhibit the ATP-sensitive K^+ channels, leading to insulin secretion over the short term but impairing insulin production with chronic drug treatment. Several groups have reported elevated insulin concentrations in patients treated with second-generation antipsychotics (Melkersson *et al.*, 2000; Newcomer *et al.*, 2002; Yazici *et al.*, 1998), which would be consistent with this proposed mechanism.

A number of different neurons distributed over several major brain regions are involved in the monitoring and control of systemic glucose concentrations. In the context of schizophrenia, one such circuit involves GABAergic (gamma aminobutyric acid) neurons in the striatum and glucose-sensitive dopaminergic neurons in the substantia nigra (Levin *et al.*, 2002). Functional activity of these dopaminergic neurons is modulated by glucose and antipsychotic drugs. This might explain the observation that movement disorders, especially tardive dyskinesia, are observed more frequently in diabetic patients or patients with high blood glucose levels who are treated with antipsychotic medications (Mukherjee *et al.*, 1985). As mentioned previously, there is some evidence that schizophrenics have a higher rate of diabetes than normal individuals. Perhaps there is a connection between the two that stems from defective glucose-sensitive circuits in the brain that include dopaminergic and GABAergic neurons in the nigro–striatal pathway.

C. Effects on Signaling Pathways: Phospholnositide 3-Kinase/Akt

Recently our group showed that several second-generation antipsychotic drugs stimulate phosphorylation (activation) of kinase-signaling pathways that include Akt and the mitogen-activated protein kinases (MAPK), ERK1/2 (Lu *et al.*, 2004). Akt and ERK regulate a variety of downstream targets involved in cell growth, differentiation, maintenance of cell size, and anabolic processes (Hajduch *et al.*, 2001; Kyosseva, 2004; Lawlor and Alessi, 2001). Notably, Akt is a major effector of insulin-mediated signaling by enhancing the recruitment of GLUTs to the cell surface and increasing expression of glucose-6-phosphate dehydrogenase (G6PDH), the major rate-limiting step of the pentose phosphate pathway (PPP). Upstream of Akt is phosphphatidylinositol 3-kinase (PI3K). Activation of PI3K is required for the phosphorylation of Akt induced by antipsychotic drugs (Lu *et al.*, 2004). Interestingly, phosphatiylinositol kinases regulate the ATP/sulfonylurea–sensitive K^+ channel via production of phosphatidylinositol phosphates that affect channel opening (Baukrowitz and Fakler, 2000). Consequently, secretion of insulin is affected by PI3K and by input from glucose-sensing neurons. Thus, antipsychotic drugs, by activating PI3K, may disturb glucose sensing in various tissues and directly affect insulin secretion by the pancreatic β cells.

Additional outcomes may result from drug-induced activation of Akt. A major role of Akt in insulin-responsive tissues is regulation of glucose metabolism, including glucose uptake via GLUTs in the plasma membrane and utilization via the PPP. Recent data from our laboratory suggest that antipsychotic drugs interfere with Akt activation in response to insulin. For these studies, 3T3-L1 preadipocytes were incubated in the absence or presence of olanzapine for 18 hours prior to addition of insulin. Normally, insulin elicits rapid (within 10 minutes) phosphorylation of Akt (Fig. 1A). However, after an 18-hour exposure to antipsychotic drug, there was a greatly diminished response to insulin. Quantification of phosphorylated Akt by enzyme-linked immunosorbent assay (ELISA) revealed a significant reduction in Akt activation by insulin subsequent to the 18-hour preincubation period with olanzapine (Fig. 1B). We have observed a similar reduction in the response to nerve growth factor in PC12 cells incubated with antipsychotic drugs (unpublished observations). One possible scenario is that activation of Akt by drugs produces desensitization or other down-modulation of the Akt pathway with long-term exposure. Chronic treatments that lead to phosphorylation of Akt on Ser473 are associated with inactivation of signaling via the insulin receptor–subunit and insulin resistance (Morisco *et al.*, 2005). If this occurred in human patients, the end result would be a decrease in insulin sensitivity, a condition associated with the development of diabetes. It will be important in future studies to explore possible mechanisms involved in the cross-regulation between drug and insulin signaling via Akt. Moreover, these

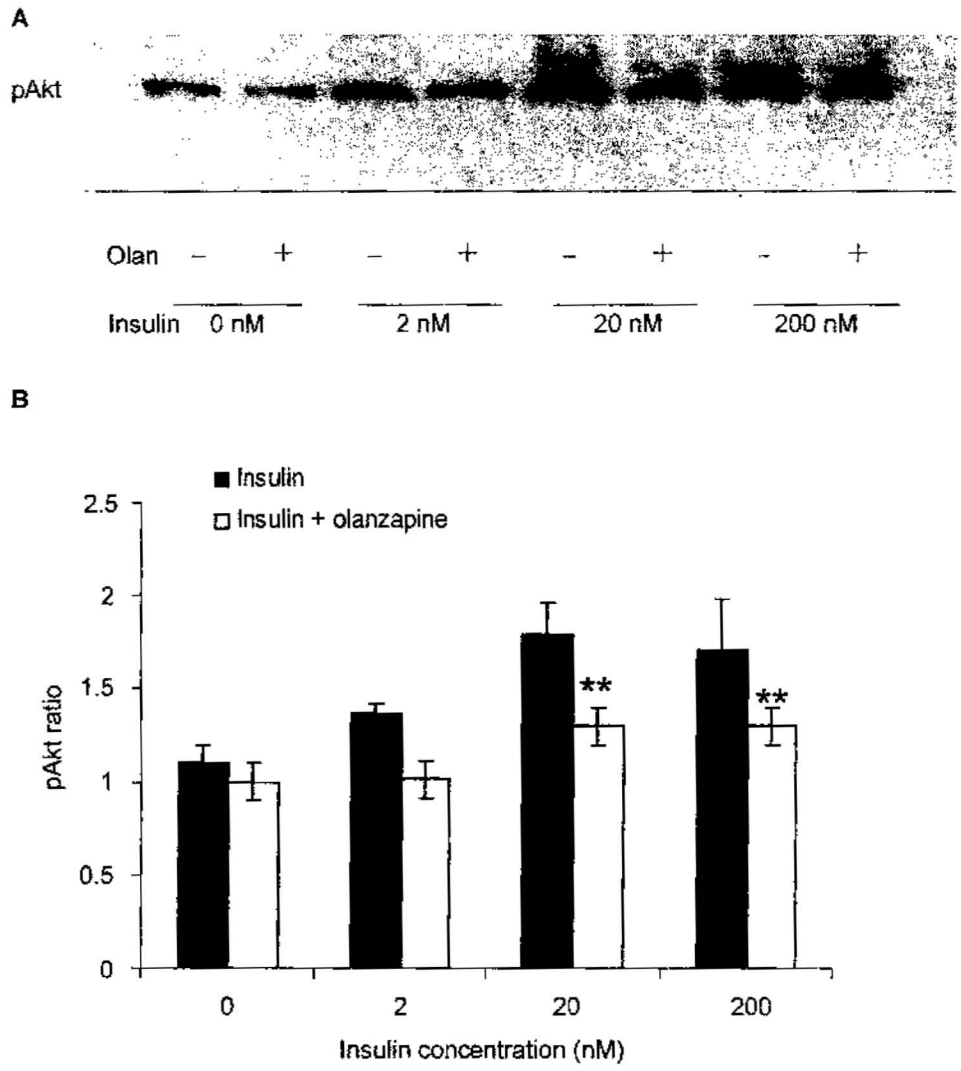

FIG. 1. Effect of olanzapine on the insulin response. 3T3-L1 cells were exposed to vehicle (solid bars) or olanzapine (50 μM; open bars) as described in the text and cell extracts were then prepared 10 minutes after the addition of insulin to the cultures. Phosphorylated Akt (Ser473) was detected with specific antibodies (Cell Signaling Technology; Beverly, MA) by western blot analysis (A) or with an ELISA kit (BioSource; Camarillo, CA) (B). The data in (B) were first normalized on the basis of total protein and are expressed in relation to the values of control samples from cells cultured in the absence of olanzapine or insulin. The asterisks indicate significant differences from the cells incubated with insulin alone (**$p < 0.01$; N = 3 experiments).

observations may have clinical relevance in that there may be an interaction between the timing of drug dose relative to meals such that prior exposure to peak levels of drug reduces the sensitivity of tissues to insulin that is induced after a meal some hours later.

D. Regulatory Balance Between Akt and AMP Kinase

In addition to insulin/PI3K/Akt, another pathway regulates glucose transport, especially in response to exercise and hypoxia, namely, the 5′-adenosine monophosphate (AMP)-activated kinase (AMPK; Hardie *et al.*, 2003; Rutter *et al.*, 2003). AMPK is itself activated by phosphorylation in response to a decrease in the ratio of cellular ATP/AMP and other signals (Hardie *et al.*, 2003; Lizcano *et al.*, 2004). AMPK appears to act as a fuel gauge whose major purpose is to increase the level of ATP in the cell via regulation of energy metabolism. Although AMPK stimulates glucose transport, which is similar to Akt, in most respects AMPK opposes the actions of Akt in cells and is involved in energy conservation and ATP production. Thus, AMPK inhibits lipid and cholesterol biosynthesis, glycogen formation, protein synthesis, and lipolysis, while it stimulates glycolysis and fatty acid oxidation and enhances insulin sensitivity (Carling, 2004; Hardie *et al.*, 2003; Rutter *et al.*, 2003). Therefore, a reduction in AMPK activity would be expected to produce a decrease in insulin sensitivity and an increase in fatty acid synthesis, which are two features of the metabolic syndrome induced by antipsychotic drugs. AMPKα2 knockout mice exhibit high glucose levels after feeding or glucose challenge and significant elevation of free fatty acids in both the fasted and fed states (Viollet *et al.*, 2003). It was suggested that hyperglycemia develops in these mice as a consequence of increased activity of the sympathetic nervous system, which controls various aspects of glucose metabolism including the insulin response (Nonogaki, 2000). Interestingly, expression of constitutively active AMPK in the medial hypothalamus of mice with recombinant adenoviruses significantly increased food intake and body weight (Minokoshi *et al.*, 2004), which is consistent with central nervous system (CNS)-regulatory mechanisms related to metabolic control that sense a shift in the ATP/AMP ratio.

Preliminary data from our laboratory suggest that olanzapine treatment for 30 minutes stimulates phosphorylation of AMPK in PC12 cells (data not shown). The activation of AMPK by olanzapine was comparable or superior to that produced by 5-aminoimidazole-4-carboxamide riboside (AICAR), a well-established pharmacological activator of this pathway (Corton *et al.*, 1995). If similar activation by olanzapine occurred in glucose-sensing neurons in the hypothalamus, this might lead to an increase in food consumption, weight gain, and sympathetic stimulation of glucose mobilization by peripheral tissues. Finally, AMPK is an attractive candidate to explain some of the observed metabolic disturbances because it is positioned to regulate both glucose and fat metabolism, which are both abnormal in many patients treated with second-generation antipsychotic drugs.

III. Metabolic Effects: Lipid Disturbances and Weight Gain

In addition to their effects on glucose metabolism, antipsychotic drugs produce abnormalities in triglyceride and cholesterol levels and significant weight gain in some patients. It seems likely that there is a connection between the lipid–weight gain effects of the antipsychotic drugs and their adverse effects on glucose regulation. The existence of a glucose–fatty acid cycle was established more than 40 years ago (Randle *et al.*, 1963). This cycle refers to the interrelationship between glucose metabolism and fatty acid levels in man. According to this scheme, uptake of glucose by cells regulates the release of fatty acids for use as fuel. Conversely, elevated concentrations of free fatty acids and ketone bodies in blood inhibit glucose metabolism and alter insulin sensitivity in various tissues. The glucose–fatty acid cycle is considered a rudimentary system for the regulation of fuel utilization that functions independently of hormonal control (Randle *et al.*, 1963). The effects of an antipsychotic drug on one aspect of this cycle will necessarily affect regulation of the other metabolic component. Interestingly, Melkersson *et al.* (2000) reported a close correlation between blood glucose levels and triglyceride and cholesterol levels in patients treated with olanzapine. Furthermore, the fact that the amount of visceral fat correlates with glucose intolerance and insulin responsiveness provides support for the interdependence of glucose and fat metabolism (Despres *et al.*, 1989). The balancing act between the use of glucose and fat for energy takes place in the larger context of a balance between anabolic and catabolic processes related to energy homeostasis. Schwartz *et al.* (2003) recently suggested that overall the system is tilted toward weight gain, which is consistent with earlier notions of "thrifty" genes that promote efficient storage of energy to withstand periods of food deprivation (Neel, 1962). However, in the face of high-fat Western diets, these thrifty genes and the anabolic bias in the system encourage weight gain and impair glucose regulation. Therefore, it is not surprising that many drugs induce significant weight gain and metabolic disturbances in patients because the inherent bias means that a small change in this same direction (induced by drugs) is sufficient to produce large cumulative effects over time.

The coordinated regulation of glucose and fatty acid metabolism is accomplished through several major mechanisms. Elevated glucose levels in blood normally lead to insulin secretion, a decrease in lipolysis, and an increase in the synthesis of fatty acids and triglycerides. A subsequent rise in fatty acids and triglycerides shifts metabolism in muscle and other responsive tissues to fatty acid oxidation (Randle, 1995; Randle *et al.*, 1963). This is accompanied by an increase in ATP and citrate, which are allosteric modulators of phosphofructokinase, a limiting enzyme of glycolysis (Randle, 1980). At the same time, an increase in the acetyl CoA/CoA ratio inhibits pyruvate dehydrogenase through both direct and indirect actions (Randle, 1980). The net effect is a decrease in glycolysis and

further glucose metabolism. Moreover, the increase in fatty acid oxidation is associated with inhibition of glucose uptake into muscle and relative insulin insensitivity. This situation reverses as lipid stores are utilized and with a rise in blood glucose levels after the next meal.

One additional connection between glucose and lipid metabolism is noteworthy: the dependence of fatty acid synthesis on the PPP. The PPP uses glucose to provide precursors for nucleotide synthesis and in the process generates NADPH, which is essential for various cell functions including fatty acid synthesis (Baquer *et al.*, 1988; Wood, 1986). Consequently, there is tight linkage between glucose metabolism via the PPP and the rate of lipogenesis in adipocytes (Kather *et al.*, 1972). From this perspective, the metabolic effects of antipsychotic drugs could be viewed as drug-induced hyperglycemia driving lipid synthesis (especially triglycerides) or alternatively as drug-induced upregulation of lipid synthesis, which mobilizes glucose to sustain the PPP. In view of the interrelationships between glucose and lipid metabolism outlined here, this is ultimately a dubious distinction.

Regardless of the precise mechanisms involved in the metabolic effects of the antipsychotic drugs, weight gain results from a person ingesting on a consistent basis more calories than he or she burns. This leads to an accumulation of fat and body mass over time. Theoretically, an imbalance between intake and consumption in response to drug treatment may arise from one of two conditions: there is an increase in caloric intake or a decrease in energy expenditure. There is little evidence that either of these situations dominates in the case of antipsychotic-induced weight gain. Therefore, we presume that both processes play a role in the metabolic effects of these drugs.

A. Clinial Observations and Scope of the Problem

Case reports of weight gain induced by the second-generation antipsychotic drug, clozapine, appeared shortly after introduction of this drug into clinical practice (Cohen *et al.*, 1990; Leadbetter *et al.*, 1992; Povlsen *et al.*, 1985). Although the problem of weight gain is typically associated with the second-generation drugs, conventional first-generation medications, including chlorpromazine and thioridazine, were also reported to cause significant weight gain in some patients (Allison *et al.*, 1999; Brady, 1989; Kalucy, 1980). Data from meta-analysis by several groups indicated that the prevalence of weight gain in patients treated with antipsychotic drugs ranged from 10–90% for those drugs with weight gain liability (Allison *et al.*, 1999; Russell and Mackell, 2001; Zimmermann *et al.*, 2003). Among the second-generation atypical antipsychotic drugs, clozapine and olanzapine produced the greatest weight gain with around 40% of patients adding more than 7% of their initial body weight. Risperidone and quetiapine produced significant weight gain in smaller percentages of patients, estimated in the range of 10–30%, whereas the newest drugs, ziprasidone and aripiprazole, stimulated weight gain in

~7–10% of patients (Russell and Mackell, 2001; Wirshing, 2004). The latter two drugs were considered weight neutral (American Diabetes Association, Consensus Statement, 2004; Russell and Mackell, 2001; Wirshing, 2004). Among the older conventional drugs, thioridazine, chlorpromazine, and thiothixine induced the greatest weight gain, whereas molindone has been reported to produce weight loss in patients (Allison *et al.*, 1999; Brady, 1989; Kalucy, 1980). Haloperidol was found to produce minimal weight gain in the meta-analysis of Allison *et al.* (1999). It is possible that some of the weight gain observed in these studies was secondary to an improvement in symptoms and the return of a healthy appetite. We favor this explanation for the instances of weight gain in patients taking the weight-neutral drugs, including ziprasidone, aripiprazole, and haloperidol.

There is some evidence that weight gain induced by antipsychotic drugs is more pronounced in younger patients, especially adolescents (Kelly *et al.*, 1998; Theisen *et al.*, 2001). However, this may, in part, be due to the lower baseline weight and greater potential for growth in this population. Most of the weight gain with antipsychotic drugs occurs in the first 4 months of therapy with a plateau observed thereafter for some medications (Umbricht *et al.*, 1994; Wetterling and Muessigbrodt, 1999). Clozapine and olanzapine appear to produce more prolonged and steady weight gain in patients (Henderson *et al.*, 2000; Wirshing, 2004). It is not uncommon for patients to add as much as 10–15 pounds over the course of treatment, although weight gain >10% of initial body mass is less frequent. Nevertheless, even modest weight gain is associated with an increased risk of cardiovascular disease, diabetes, stroke, and other serious complications (Almeras *et al.*, 2004; Fontaine *et al.*, 2001).

In addition to weight gain, the antipsychotic drugs produce a significant disturbance in lipid metabolism, most frequently hypertriglyceridemia (Casey, 2004; Meyer and Koro, 2004). Dufresne and colleagues were the first to report elevation of triglycerides in patients treated with clozapine and olanzapine (Ghaeli and Dufresne, 1995, 1996; Gaulin *et al.*, 1999; Osser *et al.*, 1999). Since those initial reports, many studies have found elevated levels of triglycerides in patients treated with second-generation antipsychotics (Henderson *et al.*, 2000; Koro *et al.*, 2002; Melkersson *et al.*, 2000; Meyer, 2001; Sheitman *et al.*, 1999); some groups reported elevated cholesterol levels as well (Baymiller *et al.*, 2002; Melkersson *et al.*, 2000; Meyer, 2002). The incidence of hypertriglyceridemia in patients treated with second-generation drugs ranges from 20–50% depending on the drug with the rank ordering: clozapine > olanzapine > quetiapine > risperidone (Saari *et al.*, 2004; Wirshing *et al.*, 2002). Ziprasidone and aripiprazole produce little or no elevation of triglycerides or cholesterol in patients (Casey, 2004; Meyer and Koro, 2004). The findings with antipsychotic drugs are significant because moderately elevated levels of triglycerides are associated with an increased risk of heart disease, including myocardial infarction (Gotto, 2002; Jonkers *et al.*, 2001), whereas high levels may cause pancreatitis

(Miller, 2000; Toskes, 1990). Hypertriglyceridemia has also been implicated in insulin-resistance, exacerbation of diabetes, and metabolic syndrome (Grundy, 1998; Krentz, 2003). As might be expected, there is generally a good correlation between the lipid disturbances and drug-induced weight gain in patients (Atmaca *et al.*, 2003; Baymiller *et al.*, 2002; Henderson *et al.*, 2000; Osser *et al.*, 1999), although this is not a universal finding (Meyer, 2001).

The weight gain and hyperlipidemia observed in patients taking antipsychotics are clearly related to the medication regimen. The disturbances appear within weeks of initiation of treatment and discontinuation of drug is accompanied by a decrease in lipid levels and loss of weight (Casey, 2004; Ghaeli and Dufresne, 1995; McIntyre *et al.*, 2001). In addition, switching a patient from a drug with high weight gain/lipid liability to a drug with a safer metabolic profile is typically associated with normalization of lipid levels and weight.

Interestingly, a number of studies have found an association between weight gain and clinical improvement. Early clinical practice with chlorpromazine revealed weight gain associated with treatment response (Planansky, 1958), although others did not observe this relationship (Gordon and Groth, 1964). With the newer second-generation drugs, a correlation between weight gain and clinical improvement has been reported in patients treated with clozapine and olanzapine (Czobor *et al.*, 2002; Gupta *et al.*, 1999; Leadbetter *et al.*, 1992; Meltzer *et al.*, 2003). One study failed to find this relationship for clozapine (Umbricht *et al.*, 1994), whereas another study confirmed the association for total BPRS (Brief Psychiatric Rating Scale) scores, but not for SANS (Scale for the Assessment of Negative Symptoms) scores (Bustillo *et al.*, 1996). To explain these observations, two main schools of thought have emerged. The first posits that the biological processes affected by the drugs to produce weight gain also contribute to the normalization of brain function. The second school of thought suggests that patients whose psychotic symptoms improve are more likely to regain their appetite for food and subsequently put on more weight than unresponsive patients. Anecdotal reports of carbohydrate craving in patients treated with antipsychotic drugs tend to support the latter interpretation. Nevertheless, more thorough investigation is needed to resolve some of these issues. For example, studies exploring the mechanisms of drug-induced weight gain would benefit from knowledge that similar biochemical and/or signaling pathways are affected in the brain during the course of treatment.

B. Genetic Studies

Several excellent reviews on the relationship between genetic factors and drug-induced weight gain have recently been published; readers are referred to these articles for a more detailed account of this topic (Basile *et al.*, 2001; Correll

(−2548G/A) and weight gain. Patients with the homozygous −2548A/A genotype gained more weight while taking chlorpromazine and risperidone than patients with the G allele. This same group found increased levels of leptin in the serum of patients who gained weight while taking antipsychotics (Zhang *et al.*, 2004), as have others (Atmaca *et al.*, 2003; Melkersson and Hulting, 2001). However, Haupt *et al.* (2005) have argued convincingly against a role for leptin in the weight disturbances seen in patients treated with antipsychotics. Genetic analysis of additional patient populations treated with drugs such as clozapine and olanzapine with greater weight gain liability may help to clarify the contribution of leptin to weight gain.

Several genes have shown a trend for involvement in antipsychotic-induced weight gain: the β_3- and α_1-adrenergic receptors and TNF-α (Basile *et al.*, 2001). In the case of the β_3 adrenergic receptor, arginine substitution at amino acid 64 was associated with greater weight gain in patients treated with clozapine (Basile *et al.*, 2001). This same polymorphism was associated with metabolic disturbances, including insulin resistance and weight gain, in untreated patients (Clement *et al.*, 1995; Widen *et al.*, 1995). On the other hand, patients homozygous for cysteine at position 347 of the α_1-adrenergic receptor showed a tendency for less weight gain with clozapine (Basile *et al.*, 2001). The TNF-α gene shows an SNP at position 308G/A. Patients treated with clozapine who were homozygous for the A variant gained about twice as much weight as patients who lacked this genotype (Basile *et al.*, 2001). Although central actions of antipsychotic drugs on these receptor systems are a possibility, it is interesting to note that all three genes are expressed in adipocytes and directly affect fat cell biology. As discussed in the following text, we believe that the weight gain liability attributable to these genes is likely expressed at the level of adipocytes rather than neuronal cells. Polymorphisms in a variety of other genes have been examined, including histamine receptors, dopamine receptors, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_6 receptors, and serotonin transporters (Basile *et al.*, 2001; Hong *et al.*, 2001, 2002; Rietschel *et al.*, 1997), however, none have shown a significant association to drug-induced weight gain thus far.

C. Animal Model Systems

1. *Rats and Mice*

Information from animal studies may help to identify some of the mechanisms by which antipsychotic drugs produce weight gain and metabolic disturbances in patients. Knockout mice have already provided significant clues that are being followed up in patient studies. Mice with a functional deletion of the 5-HT_{2C} receptor are overweight due to hyperphagia with hyperinsulinemia at later stages of development (Tecott *et al.*, 1995). The mice are also prone to potentially

fatal seizures. Perhaps surprisingly, there was no hyperlipidemia and no elevation of triglycerides even when the mice were fed a high-fat diet and despite significant weight gain. These studies revealed a role for the 5-HT_{2C} receptor in the CNS regulation of appetite and suggested that knockout mice do not suffer from a general metabolic disturbance, but rather impaired sensation of satiety. By contrast, histamine H_1-receptor knockout mice develop normally at first, although with advancing age their response to leptin (suppression of food intake) is attenuated and they become hyperphagic and obese (Masaki *et al.*, 2001, 2004). Histamine H_3-receptor knockout mice have a mild obese phenotype with an increase in food intake and adiposity (Takahashi *et al.*, 2002), although another group failed to observe significant weight gain in null mice (Toyota et a., 2002). Weight gain may result from the observed decrease in locomotory behavior and reduced energy expenditure (Toyota *et al.*, 2002). Thus, histamine receptor knockout mice provide only a partial model of the metabolic abnormalities observed in patients taking antipsychotic drugs. On the other hand, mice with a deletion of the gene coding for histidine decarboxylase, the enzyme responsible for histamine synthesis, exhibit a phenotype that more closely resembles the metabolic syndrome in patients (i.e., increased visceral adiposity, glucose intolerance, and hyperleptinemia) (Fulop *et al.*, 2003). β_3-Adrenergic receptor knockout mice have a slight increase in body fat but show few metabolic abnormalities otherwise (Susulic *et al.*, 1995). If anything, free fatty acid and glucose levels in blood are lower in the β_3-receptor $-/-$ mice than wild-type controls. While tantalizing in many respects, studies of knockout mice have also been disappointing. These studies have so far failed to mimic the situation observed in patients taking antipsychotic drugs—weight gain, lipid disturbances (especially hypertriglyceridemia), and glucose intolerance—by knocking out single relevant neurotransmitter receptors.

In parallel efforts, several groups have sought to establish animal models of antipsychotic drug-induced weight gain in order to learn more about the possible mechanisms involved. The studies can be generally categorized into one of two types: (1) those that characterize acute effects of antipsychotic drugs on appetite and feeding behavior in rats or mice, and (2) studies of weight gain with longer-term drug treatment. In an early study of feeding behavior, Benvenga and Leander (1997) reported that clozapine, but not olanzapine, increased food intake in rats with acute administration, which is curious because both drugs produce significant weight gain in patients. Kaur and Kulkarni (2002) studied feeding behavior of female mice 30 minutes after injection of either conventional or second-generation antipsychotic drugs. Chlorpromazine, haloperidol, clozapine, olanzapine, and risperidone all produced significant hyperphagia in the mice, and clozapine induced significant weight gain over a 2-week treatment period; it was the only drug tested for weight gain liability. By contrast, Hartfield *et al.* (2003a) found that administration of clozapine and olanzapine 30 minutes

prior to testing increased fat intake (ingestion of a lipid-rich liquid emulsion), whereas haloperidol did not. In a follow-up study, this group reported that stimulation of fat intake by antipsychotic drugs was not mimicked by pharmacological antagonism of histamine H_1 receptors or 5-$HT_{1/2}$ receptors alone or in combination (Hartfield *et al.*, 2003b). Finally, Kirk *et al.* (2004) showed that ziprasidone suppressed the increase in food intake brought about by administration of olanzapine, despite the fact that ziprasidone is a potent inhibitor of both 5-HT_{2C} and H_1 receptors.

A more relevant model to study the actions of the antipsychotic drugs may be the induction of weight gain in rodents with chronic drug treatment. Baptista *et al.* (1987) reported that long-term administration (21 days) of certain antipsychotic drugs in rats was associated with weight gain. Haloperidol and sulpiride produced significant weight gain in female, but not male rats. In addition, chlorpromazine caused weight loss in male rats and was weight neutral in female rats. These results are opposite to what might be expected based on clinical observations, that is, chlorpromazine is associated with weight gain in patients, whereas haloperidol has modest weight gain liability. Pouzet *et al.* (2003) confirmed that haloperidol produced significant weight gain over 3 weeks of treatment in female rats, but not male rats. Olanzapine produced a similar overall response in the rats. Pouzet *et al.* (2003) concluded that Wistar rats do not offer a relevant model for the study of antipsychotic-induced weight gain. By contrast, Arjona *et al.* (2004) observed significant weight gain in female Sprague–Dawley rats after 10 days of treatment with olanzapine but not haloperidol. However, the dose of haloperidol that was used was much lower than in previous studies. Weight gain in the olanzapine group appeared to be due to an increase in food intake and a decrease in motor activity. Differences in the dosing regimens or the strain of rats may explain some of the discrepancies in these studies. Nevertheless, it appears that rats may be of limited value in the study of the metabolic effects of antipsychotic drugs (Norman and Hiestand, 1955).

Our group has observed significant weight gain in male C57Bl/6 mice treated every other day with clozapine (Dwyer and Donohoe, 2003). The data from this study are shown in Table I. Compared with control mice injected with vehicle, the clozapine-treated mice gain an additional 1.8 g over a 2-week treatment period. Although acute administration of clozapine produced significant hyperglycemia in the mice (Dwyer and Donohoe, 2003), chronic treatment with drug did not lead to sustained hyperglycemia (Table I). A recent study by Zarate *et al.* (2004) is very informative. This group treated male mice from two different strains (A/J and C57Bl/6) daily with clozapine and measured weight gain and behavioral parameters at early (3–4 days) and late (21–22 days) time points. Intriguingly, they observed weight loss over the first 5 days of treatment, whereas the behavioral effects of the drug were maximal at this same time period. Significant weight gain was observed in both strains of mice at 3 weeks, although

TABLE 1
WEIGHT GAIN IN MICE AFTER TREATMENT WITH CLOZAPINE FOR 2 WEEKS[a]

Treatment group	Weight (g ± SD)	Acute serum glucose (mg/dl ± SD)	Chronic serum glucose (mg/dl ± SD)
Control	22.3 ± 0.9	99.2 ± 17.0	120.6 ± 16.0
Clozapine (10 mg/kg)	24.1 ± 0.7[b]	196.1 ± 39.2[b]	113.3 ± 22.4

[a]Male C57Bl/6 mice (12-weeks old) were injected with clozapine every other day for 2 weeks. Twenty-four hours after the last injection, the mice were weighed and serum was obtained for determination of blood glucose concentrations (Chronic Serum Glucose). Acute Serum Glucose levels were obtained at the start of the experiment from blood samples drawn 3 hours after the first injection of drug. All drug injections were intraperitoneal and control mice were injected with vehicle alone.

[b]Significant differences from the control group ($p < 0.01$; $N = 8$).

the effects on behavioral measures had returned to baseline levels. Thus, the antipsychotic drugs may produce acute effects on behavior (perhaps including feeding) that are related to their established pharmacology, whereas their longer-term effects on weight gain and glucose metabolism may result from desensitization of the initial pharmacological response or from mobilization of additional biological pathways. These two possibilities are not mutually exclusive. In future studies, it will be important to distinguish between the contributions of acute effects of the drugs on appetitive behaviors and chronic effects on appetite regulation (CNS control) versus fundamental metabolic processes in peripheral tissues.

a. Caenorhabditis Elegans. Recent studies in the soil nematode, *C. elegans*, suggest that this model organism may prove quite useful for research on obesity. Ashrafi *et al.* (2003) and McKay *et al.* (2003) have pioneered the use of *C. elegans* to study the regulation of fat storage at the genetic level. Ashrafi *et al.* (2003) used the fluorescent, lipid-sensitive dye Nile red to visualize fat storage in *C. elegans* and RNA interference (RNAi) to characterize the role of more than 16,500 genes on the lipid storage phenotype. They identified 305 gene inactivations associated with reduced fat storage and 112 gene inactivations that caused increased fat accumulation. Some prominent examples include inactivation of dopamine receptors and fatty acid synthesis enzymes, which are associated with reduced fat storage, and inactivations of the aryl hydrocarbon receptor, PI3K, and a glucose transporter, which produce a "fat" phenotype in the animals. McKay *et al.* (2003) inactivated two transcription factors known to regulate formation of fat in mammals and showed that *C. elegans* lacking these factors displayed a lipid-depleted phenotype or *lpd*. By reverse genetic screens (RNAi induction of *lpd*), they identified additional genes that regulated fat accumulation.

Importantly, they showed that 7 out of 8 of these genes are expressed in mammals and have similar functional roles across species.

Based on the success of these groups, we sought to determine whether *C. elegans* would respond to antipsychotic drugs with an increase in lipid accumulation in fat-storing cells. If so, the relative ease of genetic manipulation in this system may allow identification of the biological pathways involved. For these studies, animals at the first larval stage (L1) were transferred to culture plates seeded with bacteria and containing either antipsychotic drug or solvent (dimethyl sulfoxide [DMSO], control). After 2 days, the animals were rinsed off the plates, washed, fixed in 1% paraformaldehyde, and subjected to two freeze-thaw cycles. They were then stained with the lipophilic dye, Sudan black, washed several times with M9 buffer, and observed under the light microscope. The photomicrographs in Fig. 2 show that treatment with both clozapine and olanzapine produced greater staining with Sudan black than the control conditions, which indicates a relative increase in lipid stores. We wished to confirm these observations by examining the effects of olanzapine on the accumulation of Nile red in lipid deposits in *C. elegans*. For these experiments, L1 animals were cultured on seeded plates that contained agar with Nile red (0.05 μg/ml) in the absence or

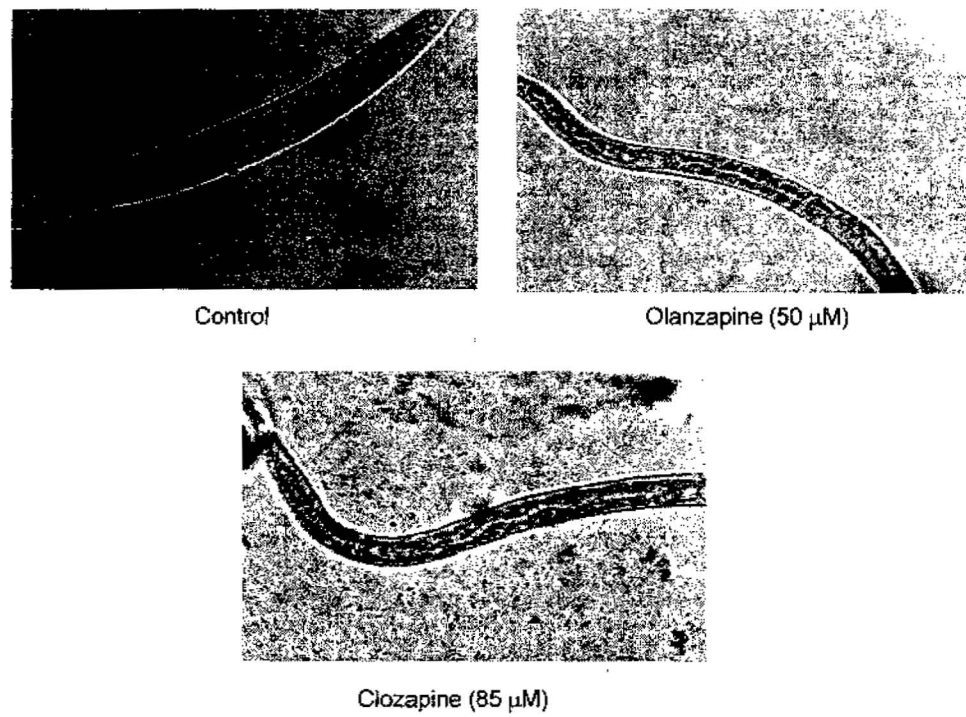

FIG. 2. Antipsychotic drugs induce lipid accumulation as measured by Sudan black staining. The photomicrographs were obtained after 48 hours of treatment with vehicle (DMSO) or drugs at the concentrations indicated and staining with Sudan black.

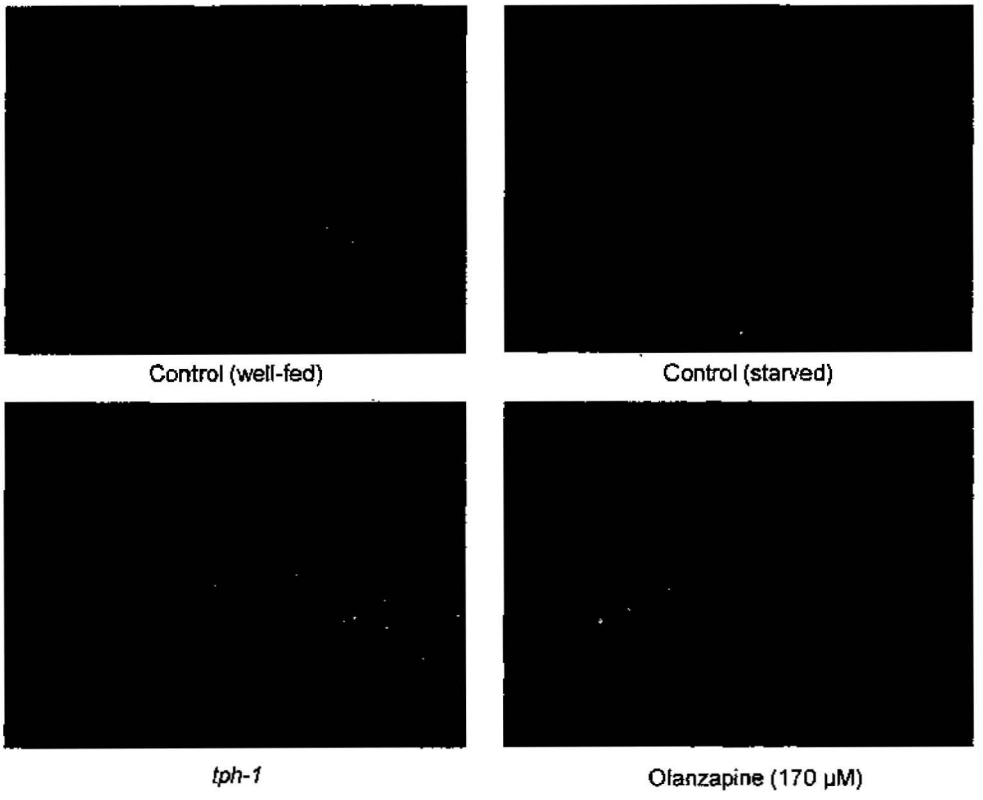

FIG. 3. Effect of olanzapine on the accumulation of Nile red in lipid stores of *C. elegans*.

presence of olanzapine (170 μM). As a positive control, we used *tph-1* animals that, due to a deficiency in serotonin, accumulate significant amounts of lipid (Sze *et al.*, 2000). At the L4 stage, the animals were paralyzed with 50 mM sodium azide and were examined for dye accumulation with a fluorescence microscope. As expected, the *tph-1* animals showed an increase in Nile red staining (reflecting the size of lipid stores) compared with well-fed and starved control animals (Fig. 3). Animals treated with olanzapine also stained more brightly with Nile red than the controls (Fig. 3).

These initial studies of drug-induced accumulation of lipophilic dyes encouraged more in-depth analysis of the response. Olanzapine was tested over a range of concentrations for its ability to stimulate accumulation of Nile red. Accumulation was quantified by digital analysis of fluorescence images and the results are summarized in Fig. 4A. Animals (20–30) from two separate plates were analyzed for mean fluorescence intensity compiled over equivalent anatomical areas. As a positive control, the *tph-1* mutant was analyzed and showed a significant elevation (1.5- to 2-fold) of staining compared to control animals. Olanzapine produced a dose-dependent increase in the accumulation of Nile

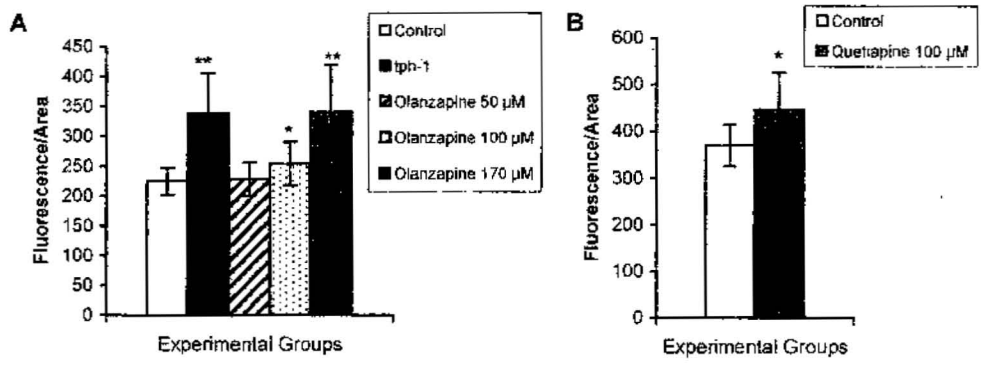

FIG. 4. Quantification of Nile red staining in *C. elegans* in response to antipsychotic drugs. Animals were exposed to Nile red in the absence (control and *tph-1*) or presence of drugs at the concentrations indicated. After 48 hours, animals (N = 40–60) from each group were analyzed for mean fluorescence over equivalent anatomical areas. The data were averaged and significant differences from the control group are indicated by asterisks ($*p < 0.05$; $**p < 0.01$).

red fluorescence, which reached significance at 100 μM and above. In addition, quetiapine induced significant accumulation of Nile red in *C. elegans* (Fig. 4B). The response to quetiapine was somewhat less than to olanzapine. Preliminary studies showed that fluphenazine, which is not associated with weight gain in patients, did not stimulate the accumulation of Nile red in the animals. Thus, several different antipsychotic drugs that are associated with weight gain and lipid disturbances in patients promote the accumulation of lipid-sensitive dyes in *C. elegans*. There are no obvious changes in feeding behavior, although there is a tendency for animals exposed to clozapine to spend less time on the bacterial lawn, which argues against an increase in food consumption as a contributing factor in lipid deposition in cells. *C. elegans* appears to represent a valuable model system for characterization of the mechanisms involved in the metabolic disturbances induced by antipsychotic drugs.

IV. Possible Targets of Antipsychotic Drugs

A. Established Pharmacology

The second-generation or atypical antipsychotic drugs tend to bind with high affinity to a wider variety of neurotransmitter receptors than the older conventional drugs and generally display greater antagonism at serotonergic receptors as judged by the ratio of antagonism of serotonergic versus dopaminergic receptors (Deutch *et al.*, 1991; Meltzer, 1999). This profile may contribute to the metabolic

liability of these drugs; however, it must be remembered that conventional dugs, including chlorpromazine and thioridazine, produce similar adverse effects. Thus far, there is little evidence that connects the actions of the antipsychotic drugs at a particular neurotransmitter receptor to the drug-induced hyperglycemia and diabetes in patients. This may be due in part to the fact that glucose abnormalities induced by the drugs are much less common than weight gain and are therefore more difficult to study at the population level. The existence of the glucose–fatty acid cycle means that at some level there is a connection between weight gain/lipid abnormalities and impaired glucose regulation. This connection is likely to include a common biochemical origin.

In terms of weight gain liability, analysis from various studies, including correlational data, genetic risk analysis, and gene deletion studies in mice, points to a possible role for several major established drug targets, including H_1, 5-HT_{2C}, β_3-, and α_1-adrenergic receptors. Each candidate has particular merits, but also striking exceptions that cast serious doubt that drug actions at a single receptor account for the weight gain and lipid and glucose disturbances. The importance of the histamine H_1 receptor in drug-induced weight gain has been touted by some groups (Kroeze *et al.*, 2003; Wirshing *et al.*, 1999) and questioned by others (Goudie *et al.*, 2003). Two separate studies found no association between genetic polymorphisms in the H_1 receptor gene and drug-induced weight gain (Basile *et al.*, 2001; Hong *et al.*, 2002). In addition, most H_1 receptor antagonist drugs that are used clinically to treat allergies are not associated with significant weight gain, and in fact the H_1 antagonist with greatest reported weight gain liability (astemizole) does not enter the CNS (Kaliner, 1992). H_1 Receptor knockout mice show no significant metabolic differences from control mice until about 30 weeks of age, after which time they gradually begin to gain weight and show evidence of impaired responsiveness to leptin (Masaki *et al.*, 2003, 2004). The weight gain appears to arise mainly from hyperphagia and altered feeding behavior (Masaki *et al.*, 2004). There is no significant change in the levels of serum triglycerides, free fatty acids, or glucose in the H_1-receptor −/− strain. As discussed earlier, mice with a deletion of the gene encoding histidine decarboxylase ultimately display a metabolic syndrome characterized by increased visceral adiposity, hyperinsulinemia, hyperleptinemia, and impaired glucose tolerance (Fulop *et al.*, 2003). However, these mice develop normally for the first 3–4 months and triglyceride and cholesterol levels remain normal even when other metabolic disturbances are clearly manifested. The weight gain in these mice appears to be related more to changes in feeding behavior, the sleep–wake cycle, and thermoregulation. Finally, the increased intake of lipid-rich emulsions that is induced in rats by antipsychotic drugs is not mimicked by administration of H_1-receptor antagonists (Hartfield *et al.*, 2003b).

The 5-HT_{2C} receptor has been a leading candidate to explain the drug-induced weight gain because clozapine and olanzapine are potent antagonists at this receptor and because animals lacking functional 5-HT_{2C} receptors are overweight and store more fat in adipose tissue (Tecott *et al.*, 1995). However, the substantial weight gain in these mutant mice is mainly due to hyperphagia and plasma levels of glucose, free fatty acids, and insulin remain normal at 12–14 weeks of age. Older mutant mice with significant weight gain eventually developed impaired glucose tolerance and reduced responsiveness to insulin and leptin; however, triglycerides and fatty acids remained normal (Nonogaki *et al.*, 1998). Another limitation to the 5-HT_{2C} receptor as the main mechanism for drug-induced weight gain concerns the relative affinity of antipsychotics for this receptor. Ziprasidone has a greater affinity for the 5-HT_{2C} receptor than clozapine, chlorpromazine, and risperidone, yet it produces much less weight gain in patients. On the other hand quetiapine, which has a low affinity for 5-HT_{2C} receptors, induces moderate weight gain. Although Reynolds *et al.* (2002, 2003) reported a significant association between antipsychotic-induced weight gain and the presence of an SNP in the 5-HT_{2C} receptor gene, two other groups failed to replicate this finding (Basile *et al.*, 2002; Tsai *et al.*, 2002).

The α_1- and β_3-adrenergic receptors have been proposed as possible drug targets involved in weight gain in patients. Basile *et al.* (2001) found a trend toward an association between weight gain with clozapine and an Arg347Cys polymorphism in the α_{1A}-adrenergic receptor. Kroeze *et al.* (2003) reported a correlation between α_{1A}-receptor antagonism and weight gain liability for an extensive panel of antipsychotic drugs. However, α_{1A}-receptor knockout mice show no weight gain or metabolic abnormalities (Tanoue *et al.*, 2003). Moreover, olanzapine, which has one of the highest weight gain liabilities, is a weaker antagonist of α_{1A}–receptors compared to ziprasidone and aripiprazole, which are weight neutral (Kroeze *et al.*, 2003). The β_3-adrenergic receptor is involved in regulation of adipocyte metabolism (Emorine *et al.*, 1994), and a Trp64Arg mutation in this receptor is implicated in insulin resistance and weight gain (Clement *et al.*, 1995; Widen *et al.*, 1995). A trend toward association of this genotype with clozapine-induced weight gain has been reported (Basile *et al.*, 2001). However, most of the antipsychotic drugs are exceedingly weak ligands at β-adrenergic receptors. Moreover, disruption of the β_3-adrenergic receptor gene is accompanied by modest metabolic changes in mice that consist mainly of increased adiposity. Weight gain and disturbance of serum lipid and glucose levels are not observed. It remains to be seen whether other receptors that are targeted by antipsychotic drugs, especially muscarinic receptors, are the major site of action for drug-induced weight gain.

Thus, it does not appear that the actions of antipsychotic drugs at a single receptor adequately account for the weight gain observed in patients. It has been suggested that combined effects of the drugs at two or more neurotransmitter

receptors may be required to explain the adverse metabolic effects (Casey and Zorn, 2001; Meltzer *et al.*, 2003; Mueller *et al.*, 2004). This is a distinct possibility; however, it is worth noting that many other drugs are also associated with weight gain and adverse metabolic effects in patients. This includes older tricyclic antidepressants, glucocorticoids, Ca^{++} channel blockers, and protease inhibitors (Kalucy, 1980; Montastruc and Senard, 1992; Pijl and Meinders, 1996; Wirshing *et al.*, 2002). Two possibilities can be entertained: (1) each class of drug has a unique mechanism of action with respect to induction of weight gain, or (2) there may be a common mode of action for many of the offending drugs. We favor the latter possibility. It seems unlikely that one of the neurotransmitter receptors mentioned here will constitute that common thread. Rather, we feel that it may be more fruitful to consider alternative mechanisms that might help to explain the weight gain and metabolic effects produced by a wide array of drugs.

B. Novel Pharmacological Actions

Previously, we showed that antipsychotic drugs inhibit glucose transport in neuronal and other cell types by interacting directly with the GLUT protein (Ardizzone *et al.*, 2001; Dwyer *et al.*, 1999a,b). We suggested that interference with glucose transport may contribute to the emergence of metabolic disturbances in patients taking antipsychotic drugs (Ardizzone *et al.*, 2001; Dwyer *et al.*, 1999b, 2001). Recent studies of knockout mice with a deletion of the insulin-regulated glucose transporter, GLUT4, provide evidence that supports this suggestion. Although homozygous GLUT4 null mice fail to thrive and die very early, heterozygous knockout mice develop diabetes and other metabolic abnormalities (Stenbit *et al.*, 1997). Moreover, when GLUT4 is specifically ablated in adipose tissue, the mutant mice exhibit insulin resistance, elevated blood glucose levels, hyperinsulinemia, and even severe diabetes in some cases (Abel *et al.*, 2001). Acute injection of mice with antipsychotic drugs that inhibit glucose transport produces significant hyperglycemia within 30 minutes to 1 hour (Dwyer and Donohoe, 2003). Furthermore, administration of cytochalasin B, a selective antagonist of GLUTs, induces acute hyperglycemia in mice of a similar magnitude as the antipsychotic drugs despite an absence of effect of this compound on the neurotransmitter receptors targeted by antipsychotic drugs (Dwyer and Donohoe, 2003; Dwyer *et al.*, 2002). Thus, a reduction in glucose transport by either drugs or genetic approaches is sufficient to cause hyperglycemia, insulin resistance, and even diabetes in mice. The GLUT4 heterozygous knockout mice showed normal lipid profiles for the most part, whereas elimination of a GLUT analog in *C. elegans* via RNAi promoted fat storage in these animals and produced a fat phenotype (Ashrafi *et al.*, 2003). The possibility that GLUTs and glucose metabolism represent a common mechanism for weight gain and metabolic

disturbances is strengthened by the observation that a wide variety of drugs that produce these same effects in patients (including tricyclic antidepressants, corticosteroids, Ca^{++} channel blockers, and protease inhibitors) affect glucose transport/metabolism (Dwyer *et al.*, 2002).

It is noteworthy that mice with a tissue-specific deletion of the insulin receptor in muscle display elevated triglycerides and fatty acids and increased fat mass (Minokoshi *et al.*, 2003). Therefore, the combination of decreased glucose transport (via drugs or reduction in GLUTs) in fat or other tissues and insulin resistance in muscle produces the same spectrum of metabolic abnormalities observed in patients treated with antipsychotic drugs.

This last point suggests that modulation of insulin-signaling pathways by antipsychotic drugs may contribute to the metabolic disturbances in patients. Elsewhere, we have reported that second-generation antipsychotics (including olanzapine and quetiapine) associated with weight gain and hyperglycemia activate the serine/threonine kinase Akt (Lu *et al.*, 2004). Akt is a major downstream target in the insulin-signaling pathway and is involved in recruitment of GLUTs to the cell surface and adipocyte differentiation and function. Pretreatment of 3T3-L1 preadipocytes with olanzapine reduces the subsequent activation of Akt in response to insulin (this article; Lu and Dwyer, 2005). Perhaps initial activation of Akt by drug leads to temporary desensitization of this signaling pathway at the level of the insulin receptor and reduced responsiveness to endogenous molecules including insulin. This might explain some of the metabolic effects of the antipsychotic drugs. Alternatively, the drugs may act, in part, through activation of the mitogen-activated protein kinase (MAPK) ERK1/2 (Lu *et al.*, 2004). ERK is involved in the differentiation of preadipocytes and the regulation of adipocyte function (Prusty *et al.*, 2002). Chronic activation of ERK by antipsychotic drugs might increase the number of adipocytes and their fat storage capacity while stimulating the production of triglycerides and fatty acids.

The antipsychotic drugs appear to activate Akt and ERK via G proteins, specifically G_i (Lu *et al.*, 2004). This may provide an additional clue because genetic downregulation of the $G_{i\alpha 2}$ subunit leads to impaired insulin sensitivity and glucose tolerance in transgenic mice (Moxham and Malbon, 1996). Further downstream of $G_\alpha i$/Akt signaling are the forkhead transcription factors such as AFX and FOXC2. Importantly, AFX is jointly regulated by Akt and AMPK (Yang *et al.*, 2002). Finally, FOXC2 is intimately involved in the regulation of weight gain, triglyceride production, and insulin sensitivity (Cederberg *et al.*, 2001). Perhaps the signal transduction pathways activated by the target(s) of the antipsychotic drugs converge on transcription factors that play a critical role in adipocyte biology, including FOXC2 and C/EBP.

Recent research by Ashrafi *et al.* (2003) provided additional candidate genes to explain drug-induced weight gain in patients. This group disrupted the expression of more than 16,500 genes in *C. elegans* with specific RNAi and

identified genes whose elimination produced either a thin or fat phenotype. Several particular genes were noteworthy because they have been shown to be affected either directly or indirectly by antipsychotic drugs. The list includes the aryl hydrocarbon receptor, potassium channels, a glutamate receptor, and PI3K. As discussed earlier, the *tph-1* tryptophan hydroxylase mutants also exhibit a fat phenotype, which is interesting in view of the established role of serotonin in satiety and feeding.

We suggest the following scheme to attempt to explain the metabolic disturbances caused by antipsychotic drugs. At the level of the CNS, the drugs may block H_1 and 5-HT_{2C} receptors to affect satiety and feeding, and inhibit glucose transport in specialized neurons to affect glucose sensing. Impaired glucose sensing by the brain may underlie the carbohydrate craving reported by many patients (Bernstein, 1987; Zimmermann *et al.*, 2003). Even more insidiously, the drugs produce significant adverse effects on peripheral tissues. Direct actions of the drugs on adipocytes, hepatocytes, and β-islet cells may lead to increased fat synthesis and storage, enhanced gluconeogenesis, and altered insulin secretion, respectively. The effects on these tissues may be mediated through direct drug interactions with adrenergic receptors (β_3 and α_1), GLUTs, or Akt, ERK, and AMPK signaling pathways. The net effect will be the sensation of glucose deprivation with an increase in gluconeogenesis and glucose output from the liver. In addition, impairment in Akt signaling would tilt the balance toward reduced insulin responsiveness and intermittent hyperglycemia, which would then drive the synthesis of fatty acids and triglycerides. As this vicious cycle progresses, patients begin to gain weight and some develop insulin resistance, hypertriglyceridemia, and even diabetes.

Why don't all patients taking antipsychotics gain significant weight or develop glucose intolerance? As many as 70–80% gain weight while taking antipsychotic drugs, up to 36% may develop diabetes during treatment, and glucose intolerance is widespread in patients taking these drugs. Thus, the number of patients who show no evidence of metabolic abnormalities may be fewer than imagined. In the population that fails to gain weight or develop glucose intolerance while taking antipsychotic drugs, relative resistance may be explained by several factors. First, these patients may express genetic polymorphisms in drug target gene(s) that protect against adverse metabolic effects of the drugs. Second, the full-blown emergence of weight gain and diabetes may require additional susceptibility genes besides the actual drug targets. Moreover, genetic differences related to drug metabolism and clearance may determine relative susceptibility to metabolic disturbances. Rather than attempting to attribute the drug-induced metabolic effects to receptors that are uniquely targeted by antipsychotic drugs, we wish to emphasize common mechanisms that might explain similar effects of the many different drugs (including tricyclic antidepressants, glucocorticoids,

protease inhibitors, and so on) that cause weight gain and glucose impairment in patients. A search for common ground may ultimately prove more fruitful in the identification of drug targets involved in the metabolic disturbances than the biased approach that has been applied to the problem thus far.

V. Clinical Implications

The weight gain and glucose intolerance induced by antipsychotic drugs seriously threatens patient compliance with treatment and elevates the risk of cardiovascular disease, diabetes, and stroke. Clearly, the emergence of these metabolic disturbances demands a timely response by the clinician responsible for care. Recently the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity issued a set of guidelines and recommendations regarding the monitoring of metabolic side effects of antipsychotic drugs (American Diabetes Association, Consensus Statement, 2004). The guidelines call for periodic evaluation of weight (body mass index, BMI), waist circumference, serum lipid and glucose levels, and blood pressure. If a patient gains more than 5% of his or her initial body weight or shows elevated glucose or triglyceride levels, the clinician should consider switching medications from one with a high risk for these problems to ziprasidone or aripiprazole, which appear to produce less weight gain and fewer metabolic abnormalities. However, it is not always possible to switch antipsychotic medications. Many patients who are taking clozapine have not benefited from therapy with other drugs. If they show significant clinical improvement with this drug of last resort, they may have to continue taking this medication despite the weight gain liability. Naturally, it is always good clinical practice to encourage patients to exercise and maintain a healthy diet. Some groups have reported success in limiting weight gain in patients taking antipsychotics with a comprehensive behavioral approach that includes exercise and close dietary monitoring (Menza *et al.*, 2004). In the case where a patient's psychotic symptoms are well controlled by a particular drug that is causing weight gain, treatment with adjunctive therapies may minimize the increase in weight and other metabolic effects. Nizatidine was reported to reduce weight gain in patients taking clozapine (McIntyre *et al.*, 2001). The antidiabetic drug, metformin, was reported to prevent weight gain in adolescents in response to antipsychotic drugs (Morrison *et al.*, 2002); however, this drug proved less successful in a pilot study in adult patients (Baptista *et al.*, 2001). Of course, any strategy to prevent antipsychotic-induced weight gain with the use of adjunctive medications

and Malhotra, 2004; Mueller *et al.*, 2004). We briefly summarize the major findings with special focus on those genes that showed significant associations with weight gain or a strong trend in this direction. For the most part, the genetic studies investigated polymorphisms in neurotransmitter receptors that are targeted by antipsychotic drugs and known to participate in the regulation of feeding and satiety. Several additional candidate genes have been investigated, including tumor necrosis factor-α (TNF-$\alpha\alpha$), leptin, and the cytochrome P450 metabolic enzymes CYP2D6 and CYP1A2.

The serotonin $(5\text{-HT})_{2C}$ receptor is an attractive candidate for some of the effects of the antipsychotic drugs because mice with a functional deletion of this gene are obese and because serotonergic agonists are used as weight loss agents (Curzon *et al.*, 1997; Tecott *et al.*, 1995). Two major polymorphisms in the 5-HT_{2C} receptor gene have been identified: a Cys23Ser mutation in the coding region and a single nucleotide polymorphism (SNP) −759C/T in the promoter region. Reynolds *et al.* (2002), in a study of weight gain induced mainly by chlorpromazine and risperidone, reported that patients with the −759T variant allele gained significantly less weight than patients with the −759C genotype. However, two other groups were unable to replicate this finding for clozapine-induced weight gain (Basile *et al.*, 2002; Tsai *et al.*, 2002), and one of the groups actually reported the opposite trend (Basile *et al.*, 2002). In a follow-up study, Reynolds *et al.* (2003) showed findings similar to their original work in patients treated with clozapine. Notwithstanding the inconsistencies, the −759C/T polymorphism accounts for at best about 25% of the weight gain observed in the studies by Reynolds and colleagues. The Cys23Ser polymorphism in the 5-HT_{2C} receptor showed no association with antipsychotic-induced weight gain (Basile *et al.*, 2001; Rietschel *et al.*, 1997) nor did polymorphisms in other 5-HT receptors (Hong *et al.*, 2001).

Genes related to drug metabolism could conceivably affect weight gain liability; this possibility has been evaluated in two studies. Ellingrod *et al.* (2002) reported a significant association between weight gain with olanzapine and the *1/*3 or *1/*4 genotypes for the CYP2D6 P450 enzyme. Patients who expressed the *1/*1 genotype were relatively protected against severe weight gain. The authors suggested that patients with the susceptible genotypes may have higher serum concentrations of olanzapine, although this was not verified in the study. Basile *et al.* (2001) investigated a possible relationship between CYP1A2 and weight gain in patients treated with clozapine. Although their findings were not significant, there was a trend for patients with the C/C genotype in intron 1 to gain more weight than patients homozygous for A/A at this position. Additional studies will be necessary to strengthen the case for involvement of P450 genes in susceptibility to drug-induced weight gain.

To our knowledge, the only other report of significant genetic association to drug-induced weight gain is by Zhang *et al.* (2003), who showed a relationship between a functional polymorphism in the promoter region of the leptin gene

will face the general limitation of frequent noncompliance in schizophrenic patients.

VI. Conclusions

Weight gain and metabolic disturbances are serious side effects; however, they are also indicative of a true biological response to the antipsychotic drugs. This is important because placebo effects are common in the treatment of psychiatric illness. Furthermore, some antipsychotic drugs may barely reach effective blood concentrations in patients and thus cause little weight gain because they are used at relatively low doses to avoid side effects such as extrapyramidal movement disorders or cardiac arrhythmias. Aripiprazole and ziprasidone may offer safer alternatives with fewer adverse metabolic effects; however, it remains to be seen whether they match the clinical effectiveness of clozapine and olanzapine against psychotic symptoms and cognitive deficits. Moreover, there are always patients who respond well to one drug, but not to a second one, regardless of the close pharmacological properties of the two drugs. In the future, it may be possible to develop drugs that lack the potential to produce adverse metabolic effects, but it will first be necessary to better understand how the current generation of drugs produces these problems. Of course, if the weight gain is inherent to inhibition of particular receptors (5-HT_{2C} and D_2) and inhibition of these receptors is necessary to treat psychosis, then the metabolic consequences of drug treatment may be an unavoidable risk. Genetic studies aimed at the identification of polymorphisms associated with drug-induced metabolic disturbances will continue to provide useful clues. Knockout mice and model organisms, including *C. elegans*, are also likely to be valuable resources in the quest to understand drug-induced weight gain. We believe that the most fruitful approach to identification of mechanisms involved in the metabolic effects of antipsychotic drugs will be to search in an unbiased manner for common threads shared by other drug classes that produce weight gain. This may include gene array studies, broad-based RNAi disruption of gene expression, and genetic screens in tractable organisms. Drug discovery programs focused on development of next-generation antipsychotic drugs would benefit from the inclusion of a screening program in an appropriate animal model to identify candidate compounds with liability for weight gain and/or glucose disturbances and to exclude these candidates from further consideration. Finally, as we begin to develop new antipsychotic drugs that address the neurodevelopmental insults that give rise to schizophrenia, we may find that the adverse metabolic effects have faded from view because the pharmacology of the new drugs is likely to be quite different from those in our current armamentarium.

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