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Induction of hyperglycemia in mice with atypical antipsychotic drugs that inhibit glucose uptake

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Abstract

Many antipsychotic drugs disturb the regulation of glucose metabolism in patients treated for schizophrenia. The goal of the present studies was to determine if these antipsychotic drugs produce hyperglycemia in mice in relation to their ability to interfere with glucose uptake and utilization. Male C57BL/6 mice were injected with a panel of typical and atypical antipsychotic drugs and blood glucose levels were determined periodically over a 3- to 6-h time interval. The atypical drugs, clozapine, desmethylclozapine, quetiapine, and loxapine, and the original antipsychotic, chlorpromazine, induced significant hyperglycemia in the mice in accordance with their effects on glucose transport. By contrast, haloperidol and sulpiride, which have little effect on glucose uptake, did not induce hyperglycemia. Risperidone produced a modest elevation of blood glucose levels, but only at a low dose of the drug. Cytochalasin B, a specific inhibitor of the glucose transporter (GLUT) protein, produced significant hyperglycemia in the mice. Overall, there was a strong correlation between the ability of a drug to inhibit glucose transport in vitro and its ability to induce hyperglycemia in vivo. Finally, the drugs that produced hyperglycemia in mice have been linked to the development of diabetes in patients.

Keywords: Antipsychotic drugs; Diabetes; Glucose transport; Hyperglycemia; Schizophrenia

1. Introduction

Antipsychotic drugs are widely used in the treatment of schizophrenia (Fleischhacker and Hummer, 1997; Kuperberg and Murray, 1996). Although these drugs effectively treat many symptoms of the disease, they have a number of serious adverse effects that may limit their clinical utility. The older conventional drugs (such as fluphenazine and haloperidol) produce extrapyramidal symptoms (EPS), including tardive dyskinesia in many patients (Casey, 1993; Jeste and Caligiuri, 1993). The newer atypical drugs alter metabolic function and may induce diabetes and significant weight gain during treatment (Allison et al., 1999; Dwyer et al., 2001; Wirshing et al., 1998). It is not yet known how the drugs interfere with energy metabolism in patients.

Our group has extensively characterized the effects of antipsychotic drugs on glucose transport and metabolism in neuronal cells and other cell types (Ardizzone et al., 2001; Dwyer et al., 1999a,b, 2002). Both the older typical antipsychotics, such as chlorpromazine and fluphenazine, and the newer atypical drugs, including clozapine, quetiapine, and risperidone, inhibit glucose uptake (Ardizzone et al., 2001; Dwyer et al., 1999a,b). The drugs are noncompetitive inhibitors, which affect the V_{max} but not the K_m of transport (Ardizzone and Dwyer, 2002). We have suggested that the drugs bind directly to glucose transporters (GLUTs) to inhibit the uptake of glucose (Dwyer, 2001; Dwyer et al., 2002). Interestingly, the more selective D2 antagonists, haloperidol and sulpiride, do not affect glucose transport (Dwyer et al., 1999a).

These findings suggest that there may be a connection between inhibition of glucose transport in vitro and the in vivo effects of the drugs on glucose regulation (Dwyer et al., 2001, 2002). Thus, the same drugs that block glucose transport in cultured neuronal cells generally produce hyperglycemia in patients (Dwyer et al., 2001, 2002). Interestingly, both the older drugs (chlorpromazine and fluphenazine) and the newer atypical medications (clozapine, olanzapine, and quetiapine) have been reported to elevate blood glucose

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levels in patients (Arneson, 1964; Hiles, 1956; Kamran et al., 1994; Kostakoglu et al., 1996; Thonnard-Neumann, 1968; Wirshing et al., 1998). Recently, Henderson et al. (2000) observed that more than one third of the schizophrenics treated with clozapine for 5 years developed diabetes. Therefore, drug-induced impairment of glucose regulation represents a significant liability, especially for some of the new atypical drugs.

Previously, several groups showed that chlorpromazine induced hyperglycemia in mice, rats, and hamsters following acute administration of the drug (Lindaur, 1956; Norman and Hiestand, 1955; Ryall, 1956). There was a modest elevation of fasting blood glucose levels and an impairment in the glucose tolerance test in animals injected with this drug. Lindaur (1956) speculated that the hyperglycemic effects of chlorpromazine may be due to inhibition of glucose uptake into tissues. In related studies, Norman and Hiestand (1955) demonstrated that chlorpromazine protected mice against insulin-induced coma and death, which suggested that the drug counteracted the effects of insulin rather than prevent its secretion. The various animal studies suggested that the antipsychotic drugs have additional biological effects that are not well characterized. Furthermore, the newer atypical drugs have not been evaluated for their ability to induce hyperglycemia in animals. A major objective of the present studies was to determine if inhibition of glucose transport might be one mechanism by which antipsychotic drugs produce hyperglycemia in vivo. Finally, we hope to establish a suitable animal model for investigating how the drugs induce diabetes in patients.

2. Methods and procedures

2.1. Drugs

Chlorpromazine (Thorazine), clozapine (Clozaril), dimethylclozapine, haloperidol (Haldol), loxapine (Loxitane), risperidone (Risperdal), and sulpiride were obtained from RBI/Sigma (Natick, MA). Quetiapine (Seroquel) was a gift from Astra-Zeneca. Cytochalasin B was obtained from Sigma (St. Louis, MO).

2.2. Animal studies

The Institutional Animal Care and Use Committee at LSU Health Sciences Center approved the procedures described here. Male C57BL/6 mice (8–12 weeks old) were used for these experiments because previous studies showed that this species was the most sensitive to the hyperglycemic effects of chlorpromazine (Norman and Hiestand, 1955). Furthermore, male C57BL/6 mice were particularly susceptible to developing diabetes after treatment with streptozotocin (Zielasek and Kolb, 1992). Mice were housed four per cage and were fasted overnight (18 h) prior to use in these studies. They were not fed during the course of the experiment. The mice (eight per group) were injected intraperitonally with drug (200 μl) or vehicle (200 μl; acetic acid–DMSO solution) in the case of the controls. Drugs were dissolved in DMSO (or ethanol in the case of risperidone) and were diluted in 0.05 M acetic acid for injection. Chlorpromazine, clozapine, desmethylclozapine, risperidone, haloperidol, loxapine, quetiapine, sulpiride, and cytochalasin B were evaluated in the studies described here. Drug concentrations were chosen on the basis of previous studies of hyperglycemia in mice (in the case of chlorpromazine), or on the basis of doses required to obtain behavioral effects in mice and/or rats. Although some drugs were used at doses that exceed the clinically relevant dose (e.g., risperidone), we wanted to compare similar amounts in mice because the effects of the drugs on glucose transport fall within a fairly narrow concentration range. The mice were bled at various time intervals over 3–6 h after the injection of drug.

2.3. Determination of blood glucose level

Serum was obtained from the mice and a standard amount (5 μl) was used in the assay. Glucose levels were determined with the glucose Trinder kit from Sigma. Each sample was assayed in duplicate and a standard curve was generated with multiple dilutions of glucose from 5 to 500 mg/dl. The amount of glucose in a serum sample was determined by comparison to the standard curve.

2.4. Glucose transport assay

PC12 cells were incubated in the absence (control) or presence of drug over a range of concentrations (5–200 μM) for 30 min prior to measuring glucose uptake. The transport of ^{3}H-2-deoxyglucose into the cells was assayed over 5 min as described in detail elsewhere (Ardizzone et al., 2001; Dwyer et al., 1999b). Inhibition of glucose transport was plotted in comparison to the control values and the concentration of drug that produced 50% inhibition of uptake (IC_{50}) was estimated from the data.

2.5. Statistical methods

For most of these studies, data were analyzed with Student's *t* test (unpaired) for statistical differences from control values. For linear regression analysis, Pearson's product–moment correlation coefficient was calculated.

3. Results

3.1. Confirmation of the effects of chlorpromazine in mice

For these studies, we evaluated a panel of antipsychotic drugs that inhibit glucose transport to varying degrees for their effects in mice. As a starting point, chlorpromazine (5 mg/kg) was administered to C57BL/6 mice in order to

confirm that this drug induces acute hyperglycemia in our system. For comparison, control mice were injected with vehicle alone and another group of mice received clozapine (20 mg/kg). As seen in Fig. 1A, chlorpromazine produced a highly significant elevation of blood glucose levels in the mice at all time points tested. Clozapine surpassed chlorpromazine in its ability to induce hyperglycemia (Fig. 1A and B) and, at the 30-min time point, six of eight mice had glucose levels greater than 325 mg/dl. There was a clear dose–response effect of this atypical antipsychotic drug and even a dose of 2.5 mg/kg was sufficient to produce significant hyperglycemia. This is far less than the standard daily dose of clozapine that is used clinically (Burns, 2001).

3.2. Atypical antipsychotic drugs induce hyperglycemia

Additional atypical drugs were then evaluated for their effects in mice in comparison to clozapine. As shown in Fig. 2, quetiapine and loxapine also produced moderate levels of hyperglycemia in the mice. Many of the mice in these groups had blood glucose levels well over 200 mg/dl. Risperidone showed more complex behavior than clozapine in this system. At a dose of 2 mg/kg, there was a modest, but significant, increase (40%) in blood glucose levels (Fig. 2). However, the drug did not induce hyperglycemia in the mice when it was tested at higher concentrations (20 mg/kg; Fig. 3A). This dose is about 100–200 times the normal daily dose in patients and the drug may be toxic at these concentrations. Nevertheless, this dose of risperidone was the same as the dose of clozapine that produced very high levels of blood glucose in the mice.

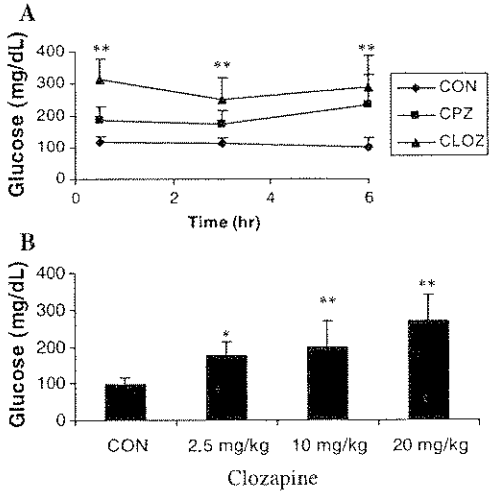

Fig. 1. Effects of chlorpromazine (CPZ) and clozapine (CLOZ) on blood glucose levels. (A) Mice (eight per group) were injected with vehicle (control, CON), CPZ (5 mg/kg), or CLOZ (20 mg/kg), and were bled at the times indicated. Blood glucose levels were measured in the Trinder assay. The averages from each group are shown together with the standard deviations (error bars). Both drugs produced significant elevation of blood glucose (** $P < .01$) at all time points. (B) Mice were treated with clozapine at the doses indicated and blood glucose levels were determined as above at 3 h. Significance levels are indicated by asterisks: * $P < .05$, ** $P < .01$.

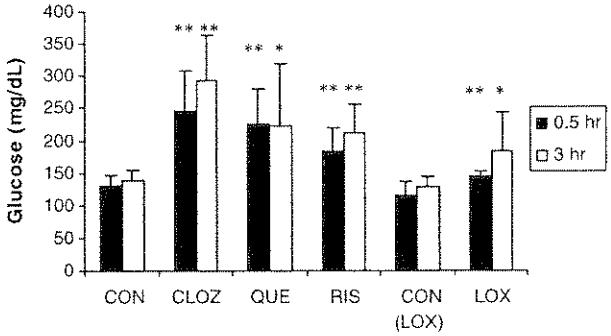

Fig. 2. Induction of hyperglycemia by atypical antipsychotic drugs. Mice (eight per group except where noted) were injected with vehicle (CON; CON LOX), CLOZ (20 mg/kg), quetiapine (QUE, 10 mg/kg; $n = 7$), risperidone (RIS, 2 mg/kg), or loxapine (LOX, 10 mg/kg; $n = 7$) and bled at the times indicated. The results and statistical analysis are represented as described in Fig. 1.

The data in Fig. 3 show that desmethylclozapine, a major metabolite of clozapine, also induced hyperglycemia in mice, whereas sulpiride, a potent dopamine D2 receptor antagonist, did not. Moreover, haloperidol, another high-potency antipsychotic drug, failed to significantly elevate blood glucose levels in the mice.

3.3. Hyperglycemia induced by inhibition of glucose transport

The antipsychotic drugs were tested for their ability to inhibit glucose uptake. An analysis of the data in Table 1

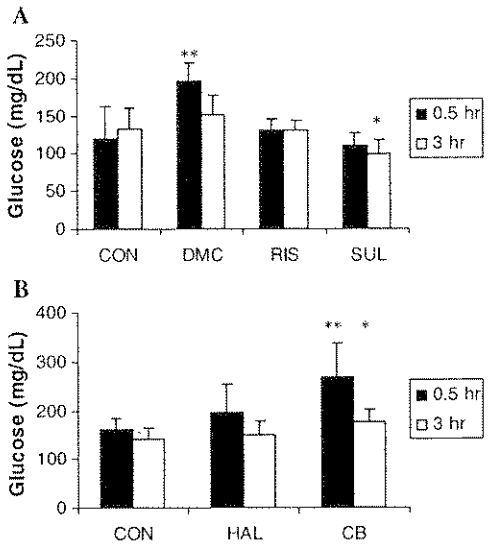

Fig. 3. Evaluation of additional antipsychotic drugs. (A) Mice (seven per group) were injected with desmethylclozapine (DMC, 10 mg/kg), RIS (20 mg/kg), or sulpiride (SUL, 10 mg/kg). (B) Mice (eight per group) were treated with vehicle (CON), haloperidol (HAL, 2 mg/kg), or cytochalasin B (CB, 20 mg/kg), and their sera were evaluated for glucose levels as before.

Table 1
Correlation between inhibition of glucose transport and induction of hyperglycemia

Drug	Glucose transport (IC_{50}; μM)[a]	Serum glucose levels (% of control)[b]
Desmethylclozapine	15	163**
Loxapine	20	127**
Clozapine (2.5 mg/kg)	30	176*
Chlorpromazine	35	159**
Risperidone (2 mg/kg)	35	140**
Quetiapine	50	174**
Haloperidol	>200	120
Sulpiride	>250	93

[a] The IC_{50} values were determined from the present studies (for loxapine and quetiapine) or from previous reports of inhibition of glucose transport by these drugs (Ardizzone et al., 2001; Dwyer et al., 1999a,b, 2002).

[b] Serum glucose levels were compiled from the 30-min time point in Figs. 1–3 and are expressed as the percentage of the control. Significant differences are indicated by asterisks.

* $P<.05$.

** $P<.01$.

confirmed that there was a good correlation ($r=0.8$; $P<.05$) between the ability of a drug to inhibit glucose transport and its ability to induce hyperglycemia in mice. Although these data focused on the 30-min time point, the atypical antipsychotic drugs also produced significant hyperglycemia at the other intervals tested, with the exception of desmethylclozapine at 3 h (Fig. 3A). To explore the relationship in more detail and to begin to identify possible mechanisms of action, we tested cytochalasin B for its ability to produce hyperglycemia in mice. Cytochalasin B is a well-characterized selective inhibitor of glucose transport, which binds directly to all mammalian GLUT isoforms (Baldwin, 1993). Unlike the antipsychotic drugs, it does not antagonize dopamine and serotonin receptors. As seen in Fig. 3B, there was a significant elevation of blood glucose levels in mice treated with cytochalasin B (20 mg/kg). At the same dose as clozapine, cytochalasin B produced average blood glucose values of 267 mg/dl compared with 314 mg/dl for clozapine. Thus, a compound, whose primary mode of action is to inhibit glucose transport, produces about the same level of hyperglycemia as the most potent antipsychotic drugs.

4. Discussion

Previously, we have shown that many antipsychotic drugs inhibit glucose transport in PC12 cells and other cell types (Ardizzone et al. 2001; Dwyer et al., 1999a,b). We have focused on PC12 cells because they represent an in vitro model of neuronal cells in culture and because they express the two major GLUT isoforms found in the brain, namely GLUT1 (endothelial and glial cells) and GLUT3 (neurons). These cells do not express GLUT4, the major insulin-sensitive isoform of peripheral tissues; however, GLUT1 is the predominant isoform in the body and drugs affect transport via this protein.

These studies sought to test the hypothesis that a compound or drug that inhibits glucose transport in vitro will produce hyperglycemia in vivo. The data presented here tend to support this hypothesis. Thus, there was a good correlation between the ability of a drug to inhibit glucose uptake and its ability to produce hyperglycemia in mice. In addition, cytochalasin B, a well-established inhibitor of GLUT proteins, produced significant hyperglycemia despite the fact that it does not affect dopaminergic, serotonergic, or adrenergic systems. Moreover, we have reported elsewhere that nimodipine, an L-type calcium channel antagonist, inhibits glucose transport and induces significant hyperglycemia in mice (Ardizzone et al., 2002; Dwyer et al., 2002).

These observations suggest that inhibition of glucose uptake by a drug may be sufficient to produce an increase in blood glucose levels, which is consistent with the earlier ideas of Lindaur (1956) concerning the effects of chlorpromazine in mice. However, the data regarding risperidone—and to some degree desmethylclozapine—suggest that inhibition of glucose transport is unlikely to be the sole explanation for the hyperglycemic effects of the drugs. Risperidone inhibits glucose transport at least as effectively as clozapine and quetiapine, yet it produces a smaller elevation in blood glucose levels in the mice. This is consistent with the effects of risperidone on glucose regulation in patients, which are intermediate between the atypicals, clozapine and olanzapine, and the conventional antipsychotic drugs (Newcomer et al., 2002). Desmethylclozapine and loxapine are two of the more potent inhibitors of glucose transport, yet they produce less hyperglycemia than clozapine and about the same hyperglycemia as chlorpromazine and quetiapine. Therefore, drugs that induce hyperglycemia may affect the regulation of glucose metabolism through additional mechanisms besides inhibition of glucose transport. Furthermore, it is possible that certain antipsychotic drugs produce opposing biological effects via separate mechanisms. For example, risperidone and loxapine may induce hyperglycemia due to inhibition of glucose transport (as expected), but may also decrease gluconeogenesis or other steps that are necessary to achieve high levels of glucose in the blood.

With this system, we have confirmed the hyperglycemic effects of chlorpromazine and have extended the observations to the newer atypical antipsychotic drugs. It appears that male C57BL/6 mice offer an attractive animal model for studying the effects of antipsychotic medications on the regulation of glucose metabolism. Thus, the drugs that produce hyperglycemia in our mouse model are the same ones that produce hyperglycemia and diabetes in patients (Dwyer et al., 2001, 2002). Moreover, drugs such as haloperidol and sulpiride, which had little effect on blood glucose levels in mice, have not been associated with induction of hyperglycemia and diabetes in patients (Dwyer et al., 2001). It is worth noting that neither sulpiride nor haloperidol inhibits glucose transport in neuronal cell types (Dwyer et al., 1999a). Clozapine, which was one of the most

potent drugs in our model system, has recently been reported to induce diabetes in as many as one third of patients treated over a 5-year time frame (Henderson et al., 2000).

Although the precise mechanism by which the drugs induce hyperglycemia is unknown, the data rule out some possibilities. The failure of haloperidol and sulpiride to raise blood glucose levels indicates that dopamine D2 receptors are not involved in the response. Although α_1-adrenergic antagonists have been reported to produce hyperglycemia in mice (Chaouloff et al., 1990), the profile of this response does not accurately match the response observed here [i.e., the hyperglycemia in response to prazosin is very modest (20% increase) and short-lived (30 min vs. 6 h or more as shown here)]. The data with cytochalasin B suggest that inhibition of neurotransmitter receptors is not an absolute requirement for induction of hyperglycemia. Furthermore, the fact that hyperglycemia is induced in mice following an overnight fast (insulin levels will be very low at this time) suggests that insulin responsiveness is not a primary target of the drugs. Moreover, hyperglycemic clamp studies in normal subjects reveal little effect of atypical drugs on the secretion or response to insulin (Sowell et al., 2002). We propose that the antipsychotic drugs may induce hyperglycemia by blocking glucose sensing in critical cells located in the brain, pancreas, and liver. The net effect might be that these cells mistakenly perceive a state of glucose deprivation and shift metabolic processes towards glucose output. In addition, the drugs may cause a global reduction of glucose utilization that further contributes to the elevation of blood glucose levels.

We have now successfully established a model system in mice that reasonably reflects the situation in patients treated with antipsychotic drugs. There are some important differences, however. Mice acutely develop hyperglycemia in response to the drugs, whereas it may take several months for diabetes to emerge in patients. Nevertheless, short-term effects of the drugs on glucose regulation have been observed in patients (Newcomer et al., 2002; Sowell et al., 2002). Weight gain and/or lipid disturbances may also contribute to the development of insulin resistance and diabetes in patients on the antipsychotic drugs. However, the emergence of diabetes in patients treated with the antipsychotic drugs is not uniformly associated with an increase in weight (Henderson et al., 2000; Haupt and Newcomer, 2001). Elevated lipids or triglycerides may help to produce some insulin resistance in patients, but other factors must also play a role in the development of overt diabetes. We have observed significant weight gain in mice treated with clozapine for 3 weeks (D.S.D., unpublished observations). Therefore, it may be possible to evaluate the role of weight gain and adiposity in the development of sustained hyperglycemia in the mice. With this system, we can begin to examine potential mechanisms for drug-induced diabetes in greater detail. A preliminary account of these findings has been reported elsewhere (Donohoe and Dwyer, 2002).

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