Chlorpromazine-Induced Glucose Intolerance in the Mouse[1] (34561)

JOHN H. MENNEAR AND TOM S. MIYA

Department of Pharmacology and Toxicology, Purdue University, Lafayette, Indiana 47906

The ability of chlorpromazine to produce hyperglycemia in laboratory animals is well documented (1–4). Similarly, this drug has been shown to produce abnormalities in carbohydrate disposition or metabolism in humans (5). This effect in humans has been reported to range from relatively mild and transient episodes of hyperglycemia to the precipitation of clinical diabetes mellitus (5). An earlier report from these laboratories was concerned with chlorpromazine-induced hyperglycemia in the rat (6). These studies suggested that the hyperglycemic response to a single dose of chlorpromazine is mediated through at least two mechanisms, the release of epinephrine from the adrenal medulla and impairment of the peripheral utilization or transport of glucose. The purpose of the present study was to extend our experiments to a second species, the mouse, and to evaluate the effect of repeated doses of chlorpromazine on blood glucose.

Methods and Materials. Male albino mice weighing 20 to 24 g (Laboratory Supply Co., Indianapolis) were used in all experiments. Prior to experimentation the mice were housed in groups of 25 with free access to food and water. Animals were sacrificed by decapitation, blood was collected in oxalated beakers, and then assayed for glucose by the glucose oxidase method.[2] Liver glycogen was measured by the method of Rerup and Lundquist (7). Differences in blood glucose or liver glycogen levels between treatment groups were assessed using the Student *t* test. All solutions were prepared daily and administered in volume doses of 10 ml/kg. Dosage levels and routes and times of administration are presented in the Results section. When fasted mice were employed, food was removed from cages 16 hr prior to experimentation.

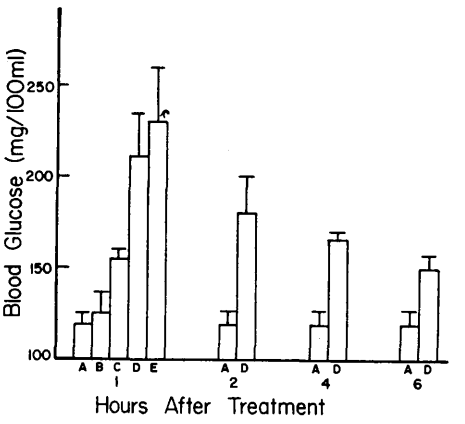

FIG. 1. Dose-response relationship of intraperitoneally administered chlorpromazine on blood glucose in mice. Each bar represents mean blood glucose values from groups of five mice. A; control, B; 1.0 mg/kg, C; 3.0 mg/kg, D; 5.0 mg/kg, and E; 10 mg/kg.

Results. The time course of chlorpromazine-induced hyperglycemia in normally fed mice is shown in Fig. 1. An intraperitoneal (ip) dose of 1.0 mg/kg of chlorpromazine failed to elevate blood glucose levels at the 1-hr interval. Doses ranging from 3.0 to 10 mg/kg, however, all produced significant and dose related elevations at this interval. With the 5.0 mg/kg dose, the peak effect was noted at the 1-hr interval and blood glucose was still elevated after 6 hr. Blood sugar levels were found to be within normal limits 16 hr after administration of the drug. On the basis of this finding the 5.0 mg/kg dose and a 1-hr-treatment interval was selected for all acute experiments with chlorpromazine.

The next experiment was conducted to assess the influence of the prandial state on the magnitude of the hyperglycemic response to

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[2] Worthington Biochemical Corp., Freehold, New Jersey.

TABLE I. Effect of Fasting on Liver Glycogen and Chlorpromazine[a] (CPZ)-Induced Hyperglycemia in Mice.

Treatment	n	Liver glycogen (% wet weight)	Blood glucose (mg/100 ml)
Normally fed			
Saline	5	4.7 ± 0.3	113 ± 10
CPZ	5	—	236 ± 20[b]
Fasted (16 hr)			
Saline	5	0.6 ± 0.2[c]	56 ± 2
CPZ	5	—	75 ± 8

[a] 5.0 mg/kg administered 60 min prior to sacrifice.

[b] Greater than normally fed control ($p < 0.005$).

[c] Less than normally fed control ($p < 0.005$).

chlorpromazine. Mice were fasted for 16 hr prior to the ip administration of 5.0 mg/kg of chlorpromazine. In this experiment liver glycogen as well as blood glucose was determined. The results of the experiment are shown in Table I. Fasting for 16 hr produced a remarkable depletion of liver glycogen. Similarly, this duration of fasting resulted in greatly reduced resting blood glucose levels. When chlorpromazine was administered to normally fed mice, blood glucose levels were raised by more than 100%; however, blood glucose levels in chlorpromazine-treated fasted mice were not significantly different from those found in saline-treated fasted mice (29% increase, $p > 0.05$). On the basis of these findings it was decided to conduct all further studies in normally feeding mice.

The effect of repeated doses of chlorpromazine on the glycemic response of mice is shown in Table II. Mice were treated with an ip dose of 10 mg/kg of chlorpromazine 18 hr prior to the 5.0 mg/kg dose and then sacrificed 1 hr after the second dose. Blood glucose levels in animals receiving the single 10 mg/kg dose 19 hr prior to sacrifice had returned to normal and the 5.0 mg/kg dose administered 1 hr prior to sacrifice produced a two-fold increase in blood glucose in non-pretreated mice. Surprisingly, however, pretreatment with the single dose of 10 mg/kg chlorpromazine completely abolished the hyperglycemic response to the second dose (132 vs. 136 mg %).

The results shown in Table III were obtained from an experiment to assess the influence of chlorpromazine pretreatment on the blood glucose responses of mice to other known hyperglycemic agents. In this experiment mice were pretreated with chlorpromazine 18 hr prior to the administration of either alloxan (75 mg/kg, iv) or epinephrine (100 mcg/kg, sc). The mice were sacrificed 45 min after the administration of alloxan and 30 min after epinephrine. It may be seen from the data summarized in Table III that the doses of alloxan and epinephrine employed in this experiment produced unequivocal elevations of blood glucose in normal animals. Also, it may be seen that under the conditions of this experiment, pretreatment with chlorpromazine failed to prevent the hyperglycemic response to either alloxan or epinephrine.

The final experiment was conducted to determine the effect of repeated doses of chlorpromazine on glucose tolerance in mice. In this experiment mice were pretreated with 10 mg/kg of chlorpromazine 24 hr prior to the administration of either a glucose load (4.0 g/kg, ip) or a combination of 5.0 mg/kg of chlorpromazine and glucose. The results of this experiment are summarized in Table IV. In preliminary experiments we found that normal mice respond to an ip dose of 4.0 g/kg of glucose with elevated blood glucose 15 and 30 min after injection and, as shown

TABLE II. Effect of Repeated Doses of Chlorpromazine (CPZ) on Chlorpromazine-Induced Hyperglycemia in Mice.

Treatment[a]			
No. 1	No. 2	n	Blood glucose (mg/100 ml)
Saline	Saline	5	136 ± 6.1
CPZ[b]	Saline	5	135 ± 8.5
Saline	CPZ[c]	5	231 ±18.[d]
CPZ[b]	CPZ[c]	5	132 ± 4.6

[a] Treatment No. 1 was followed in 18 hr by Treatment No. 2; animals were sacrificed 1 hr after Treatment No. 2.

[b] 10 mg/kg ip.

[c] 5.0 mg/kg ip.

[d] Significantly greater than control ($p < 0.01$).

TABLE III. Effect of Chlorpromazine (CPZ) Pretreatment on Alloxan and Epinephrine-Induced Hyperglycemia in Mice.

Treatment[a]			
No. 1	No. 2	*n*	Blood glucose (mg/100 ml)
Saline	Saline	5	129 ± 3.6
CPZ[b]	Saline	5	126 ± 7.1
Saline	Alloxan[c]	5	368 ± 31 [e]
CPZ	Alloxan	5	309 ± 13 [e]
Saline	Epinephrine[d]	5	205 ± 25 [e]
CPZ	Epinephrine	5	198 ± 13 [e]

[a] Treatment No. 1 was followed in 18 hr by Treatment No. 2; animals were sacrificed 45 min after alloxan and 30 min after epinephrine.

[b] 10 mg/kg ip.

[c] 75 mg/kg iv.

[d] 100 mcg/kg sc.

[e] Significantly different from controls.

in Table III, blood levels of glucose are returned to within normal limits 1 hr after treatment. When chlorpromazine was administered simultaneously with glucose in nonpretreated mice a remarkable elevation of blood glucose was observed (483 mg % vs. 92 mg %). The magnitude of this effect of chlorpromazine on glucose tolerance was significantly reduced by pretreatment with chlorpromazine 24 hr prior to the administration of glucose (268 mg % vs. 483 mg %).

Discussion. The results of these studies support our earlier suggestion that at least two mechanisms are involved in chlorpromazine-induced abnormalities in blood glucose levels. In the mouse and rat the inital glycemic response to the administration of a single dose of chlorpromazine is an elevation of blood glucose. We have found that this effect persists for at least 6 hr in the mouse. The exact mechanism of this hyperglycemic effect is not known; however, the adrenals are involved since adrenalectomy abolished it (6). Also, the effect appears to depend upon the mobilization of glycogen from the liver since we have found that 16 hr of fasting, which results in essentially complete depletion of liver glycogen, reduced the response to chlorpromazine. These findings suggest a possible epinephrine-mediated mechanism for the initial hyperglycemic response.

In the present experiments we have demonstrated that mice develop tolerance to the initial hyperglycemic producing effect of chlorpromazine. This is evidenced by the fact that the administration of one dose of chlorpromazine 18 hr prior to a second dose completely abolished the hyperglycemic effect of the second dose. Interestingly, this tolerance to chlorpromazine-induced hyperglycemia appears to be a specific phenomenon since two known hyperglycemic agents, epinephrine and alloxan, were found to induce hyperglycemia in chlorpromazine-pretreated mice. The mechanism of this tolerance is currently under investigation in our laboratories.

A second effect of chlorpromazine on carbohydrate disposition in the mouse was demonstrated by the use of the glucose tolerance test. Chlorpromazine treatment reduces glucose tolerance in mice. Blood glucose levels were nearly six times higher in mice receiving chlorpromazine plus the glucose load than in animals receiving glucose alone. Pretreatment with chlorpromazine 24 hr prior to testing partially antagonized the effect of a second dose of chlorpromazine on glucose tolerance. Blood glucose levels in the pretreated mice which received chlorpromazine plus the glucose load were only 2.5-fold higher than pretreated animals receiving only the glucose load. This difference between the two treatment groups may be due to the effect of chlorpromazine pretreatment on the

TABLE IV. Effect of Chlorpromazine (CPZ) on Glucose Tolerance in Mice.

Treatment			
No. 1[a]	No. 2[b]	*n*	Blood glucose (mg/100 ml)
Saline	Saline	5	81 ± 11
CPZ[c]	Saline—glucose[d]	5	109 ± 6.0
Saline	Saline—glucose	5	92 ± 7.0
CPZ	CPZ[e] + glucose	5	268 ± 32 [f]
Saline	CPZ + glucose	5	483 ± 58 [f]

[a] 25 hr prior to sacrifice.

[b] 1 hr prior to sacrifice.

[c] 10 mg/kg ip.

[d] 4.0 g/kg ip.

[e] 5.0 mg/kg ip.

[f] Significantly greater than respective controls and significantly different from each other.

initial hyperglycemic response to subsequent administrations of the drug rather than a reflection of an effect of the pretreatment on the peripheral disposition of glucose. In nonpretreated mice one would expect both the initial hyperglycemic response and impaired glucose tolerance to contribute to the elevated blood sugar levels. In pretreated mice only the direct influence of chlorpromazine on glucose tolerance would be evident.

Summary. Intraperitoneally administered chlorpromazine produced a dose-related increase in blood glucose levels in the mouse. The magnitude of the hyperglycemic response is related to liver glycogen levels, since fasting depleted liver glycogen and attenuated the hyperglycemic response. Mice quickly develop tolerance to the hyperglycemic effect of CPZ and 18 hr after a single dose of chlorpromazine a second dose of the drug is not hyperglycemic. Tolerance to chlorpromazine-induced hyperglycemia does not impart tolerance to the hyperglycemic effects of either epinephrine or alloxan. Chlorpromazine was also found to reduce glucose tolerance in mice, but the reduced glucose tolerance is not completely antagonized by pretreatment with CPZ.

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