Failure of *Beta*-Adrenergic Blocking Agents to Antagonize the Hyperglycemic Effect of Epinephrine in Mice[1] (35518)

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Chlorpromazine (CPZ) produces hyperglycemia and adnormalities in carbohydrate metabolism in several species including man (1–5). It has been hypothesized that CPZ-induced hyperglycemia is mediated via release of adrenal epinephrine. This is supported by the finding that adrenalectomy abolishes CPZ-induced hyperglycemia in rats (6). Additional evidence includes the fact that CPZ-induced hyperglycemia in rats is blocked by *beta*-adrenrgic blocking agents (6), which also prevented epinephrine-induced hyperglycemia in rats (7–9).

While studying chlorpromazine-induced hyperglycemia in mice, we found, contrary to our earlier findings with rats, that *beta*-adrenergic blocking agents failed to influence this response. The results of further experiments suggest a possible species difference between rats and mice with respect to the interaction between *beta*-adrenergic blocking drugs and epinephrine.

Methods and Materials Male albino mice (Laboratory Supply Co., Indianapolis), 20–24 g, were housed in groups of 25, with free access to food and water prior to experimentation.

For one experiment mice were bilaterally adrenalectomized under hexobarbital anesthesia. The animals were then maintained on 0.9% NaCl drinking water and laboratory chow for 4 days prior to experimentation.

Solutions of chlorpromazine HCl, propranolol HCl, and epinephrine Cl were prepared immediately prior to administration. Concentrations of the drug solutions were prepared to allow the administration of volume doses of 10 ml/kg. Doses were calculated on the basis of the salt of each drug.

Animals were sacrificed by decapitation, blood was collected in oxalated beakers, then assayed for glucose by the glucose oxidase method.[2] Differences in blood glucose levels between treatment groups were assessed using the Student *t* test.

Results. The effect of bilateral adrenalectomy on the glycemic response of the mouse to 5.0 mg/kg of CPZ, ip, is shown in Table I. The results of this experiment clearly show that while CPZ induces an unequivocal hyperglycemia in the intact mouse, the response to the drug is completely abolished by adrenalectomy. These finding are identical to our earlier results when rats were used (6) and suggest that in the mouse, as in the rat, CPZ-induced hyperglycemia is mediated via the adrenal glands. Also shown in Table I are the results of an experiment in which an attempt was made to antagonize the hyperglycemic effect of CPZ in intact mice with propranolol. These results show that this *beta*-adrenergic blocking agent failed to influence CPZ-induced hyperglycemia. A similar experiment was conducted using a second *beta*-adrenergic blocking agent, MJ-1999; and identical results were obtained. The findings of these experiments are in opposition to our earlier results obtained in experiments conducted with rats (6).

Since we had hypothesized that CPZ-induced hyperglycemia is mediated through the release of endogenous epinephrine, we attempted to alter epinephrine-induced hyperglycemia in mice with the *beta*-adrenergic blocking drugs. The results of this experiment are shown in Table II. Propranolol, in intraperitional doses ranging from 3.0 to 30 mg/kg failed to reduce significantly the mag-

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

TABLE I. Glycemic Responses of Intact and Adrenalectomized Mice to Chlorpromazine[a] (CPZ) and the Effect of Propranolol[b] (P) on the Response.

Treatment	n	Blood glucose (mg/100 ml ± SE)
Adrenalectomized mice		
Control	10	104 ± 7
CPZ	10	104 ± 10
Intact mice		
Control	5	130 ± 8
CPZ	5	250 ± 22[c]
+ P, 3.0 mg/kg	5	255 ± 20[d]
30 mg/kg	5	236 ± 24[d]

[a] 5.0 mg/kg, ip, 60 min prior to sacrifice.
[b] Administered 60 min prior to sacrifice.
[c] Significantly greater than control ($p < 0.01$).
[d] Significantly greater than control ($p < 0.01$), but not different from CPZ alone.

nitude of hyperglycemia produced in mice by epinephrine, 0.1 mg/kg, sc. We have reported earlier that a dose of 10 mg/kg of propranolol markedly attenuates the hyperglycemic effect of epinephrine in rats (10).

Discussion. The present results indicate that in the mouse, as well as in the rat, CPZ-induced hyperglycemia is mediated through the adrenal gland. However, the failure of *beta*-adrenergic antagonists to prevent either CPZ- or epinephrine-induced hyperglycemia in mice suggests a species-related difference with respect to the results of interactions between *beta*-adrenergic blocking drugs and epinephrine.

Several species differences in metabolic response to the catecholamines have been reported (11). Recently, we have demonstrated differences between rats and mice in their glycemic responses to the *beta*-adrenergic stimulant isoproterenol (12). Unfortunately the mechanism of these species differences is not clear. However, it does not seem likely that our findings are due to an unexpectedly rapid inactivation of the *beta* blockers by mice since these agents have been shown to produce well-defined pharmacologic effects in this species (13–15). It is possible that our results are a reflection of a species difference in susceptibility of certain adrenergic receptors to *beta*-adrenergic blockade.

TABLE II. Effect of Propranolol (P) on Epinephrine (E)[a]-Induced Hyperglycemia in Mice.

Treatment	n	Blood glucose (mg/100 ml ± SE)
Control	5	111 ± 6
Epinephrine	5	271 ± 18[b]
+ P, 3.0 mg/kg	5	241 ± 23[c]
10 mg/kg	5	279 ± 18
30 mg/kg	5	258 ± 15

[a] 0.1 mg/kg, sc, 30 min. prior to sacrifice.
[b] Significantly greater than control ($p < 0.01$).
[c] Significantly greater than control ($p < 0.01$), but not different from epinephrine alone.

Summary. Chlorpromazine-induced hyperglycemia is abolished by adrenalectomy in mice. The administration of *beta*-adrenergic blocking agents failed to alter the magnitude of the CPZ-induced hyperglycemia. Similarly, *beta*-adrenergic blockade does not influence epinephrine-induced hyperglycemia in mice. Since *beta*-adrenolytic agents block both CPZ- and epinephrine-induced hyperglycemia in rats, the results of the present studies suggest a species difference in the susceptibility of certain adrenergic receptors to *beta* blockade.

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