Chlorpromazine and Epinephrine Hyperglycemic Mechanisms

By TAGHI GHAFGHAZI*, TOM S. MIYA, J. H. MENNEAR, and R. K. CHALMERS

Chlorpromazine administration resulted in hyperglycemia in the intact, but not in the adrenalectomized, rat. However, chlorpromazine potentiated epinephrine-induced hyperglycemia in both intact and adrenalectomized animals. β-Adrenergic blockade prevented chlorpromazine-induced as well as epinephrine- and isoproterenol-induced hyperglycemia. α-Adrenergic blockade potentiated epinephrine-induced hyperglycemia. A significant reduction of tolerance to glucose loading was exhibited in both intact and adrenalectomized rats after treatment with chlorpromazine. The results indicate that the adrenals are necessary for chlorpromazine-induced hyperglycemia and that chlorpromazine impairs peripheral utilization of glucose.

PREVIOUS REPORTS in the literature have indicated the ability of chlorpromazine to produce hyperglycemia in several animal species including man. Courvoisier *et al.* (1) were the first to observe the hyperglycemic effect of chlorpromazine. After administration of chlorpromazine an increase in blood glucose levels has been observed in mice and hamsters (2), in dogs (3), and in rabbits (4, 5). Although Norman and Hiestand (2) were not able to find a significant effect of chlorpromazine on blood glucose in rats, other workers (6–8) have demonstrated this phenomenon. Hyperglycemia has also been reported during chlorpromazine therapy in humans (9, 10).

Several mechanisms are probably involved in chlorpromazine-induced hyperglycemia. It is partly the result of an indirect effect due to the release of catecholamines following the fall of body temperature produced by this drug (7). Chlorpromazine in low doses, which have no effect on body temperature, has been shown to decrease the tolerance to glucose load (11).

Chlorpromazine-induced hyperglycemia in the rat has been shown to be blocked by phentolamine, an α-adrenergic blocking agent (7). In the same species, it has been reported that the glycemic effect of chlorpromazine as well as of epinephrine could also be blocked by a β-adrenergic blocking agent such as pronethalol (8). Antonis *et al.* (12) have shown that the hyperglycemic responses to epinephrine in man can be blocked by simultaneously employing both α- and β-adrenergic blocking agents. The rise of blood glucose was not prevented by either blocking agent alone.

In this study, the effect of different adrenergic blocking agents on chlorpromazine-induced hyperglycemia was investigated. Experiments were also conducted to study the effect of concomitant administration of epinephrine and chlorpromazine in intact and adrenalectomized rats. The general objective of the study was to elucidate the mechanism of action of chlorpromazine-induced hyperglycemia.

EXPERIMENTAL

Material and Methods—Male albino Holtzman rats weighing approximately 250 g. and fasted 16–20 hr. with water *ad libitum* were employed. Blood glucose determinations were carried out by the glucose oxidase method[1] on blood taken from the orbital sinus. After bilateral adrenalectomy the animals were maintained on commercial food pellets and 0.9% saline *ad libitum* for 7 days prior to drug treatment.

RESULTS

Chlorpromazine Potentiation of Epinephrine Hyperglycemia—Graded hyperglycemic responses were obtained with 5, 10, 15, and 20 mg./kg. of chlorpromazine (Fig. 1).

The potentiating effect of chlorpromazine pretreatment on epinephrine-induced hyperglycemia is illustrated in Fig. 2. Chlorpromazine at 5 mg./kg. produced only slight hyperglycemia but significantly increased epinephrine-induced hyperglycemia.

Effect of MJ-1999[2] and Phenoxybenzamine[3] Pretreatment on Drug-Induced Hyperglycemia—MJ-

Received May 22, 1968, from the Department of Pharmacology-Toxicology, School of Pharmacy & Pharmacal Sciences, Purdue University, Lafayette, IN 47907

Accepted for publication on July 2, 1968.

Presented to the Pharmacology and Biochemistry section, APhA Academy of Pharmaceutical Sciences, Miami Beach meeting, May 1968.

Supported in part by grants MH8803 and GM15005.

* Iranian Government Fellow.

[1] Glucose oxidase enzyme (Glucostat), Worthington Biochemical Corp., Freehold, N. J.

[2] MJ-1999 [4'-(2-isopropylamino-1-hydroxyethyl) methane sulfonanilide HCl] was kindly supplied by Mead Johnson Laboratories, Evansville, Ind.

[3] Phenoxybenzamine (Dibenzyline) was kindly supplied by Smith, Kline & French Laboratories, Philadelphia, Pa.

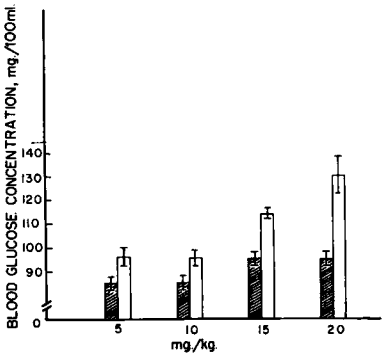

Fig. 1—Effect of intraperitoneal doses of chlorpromazine on fasting blood glucose 1 hr. after treatment. Each bar represents the average and standard errors derived from 6 animals. Shaded bars indicate control determinations.

1999 produced a significant hypoglycemia ($p < 0.005$) and blocked chlorpromazine-induced hyperglycemia (Fig. 3). Phenoxybenzamine raised blood glucose from 75 to 84 mg.% ($p < 0.1$—not significant) and did not block the chlorpromazine-induced hyperglycemia (Fig. 4). The hyperglycemia induced by isoproterenol and epinephrine was blocked by MJ-1999 pretreatment (Fig. 5).

Phenoxybenzamine alone at 10 mg./kg. produced an insignificant hyperglycemia and when administered with epinephrine, potentiated the epinephrine-induced hyperglycemia (epinephrine HCl, 30 mcg./kg., 150.0 ± 2.4 mg.% *versus* phenoxybenzamine plus epinephrine, 203.6 ± 3.6 mg.%; $p < 0.001$).

Figure 6 illustrates the lack of hyperglycemic response from chlorpromazine administration to adrenalectomized rats whereas epinephrine produced a significant hyperglycemia ($p < 0.005$). When chlorpromazine was administered prior to epinephrine, it markedly potentiated ($p < 0.001$) the epinephrine hyperglycemia. All hyperglycemic re-

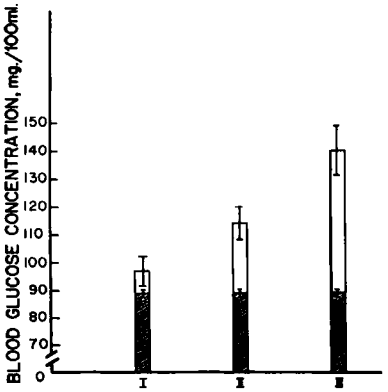

Fig. 2—Effect of chlorpromazine (CPZ) pretreatment on epinephrine HCl-induced hyperglycemia. Blood glucose determined 30 min. after epinephrine (30 mcg./kg.) and 90 min. post-CPZ (5 mg./kg.) administration. Shaded area indicates saline control blood glucose levels. Key: I, CPZ; II, Epi.; III, Epi. + CPZ. Means from 4 rats.

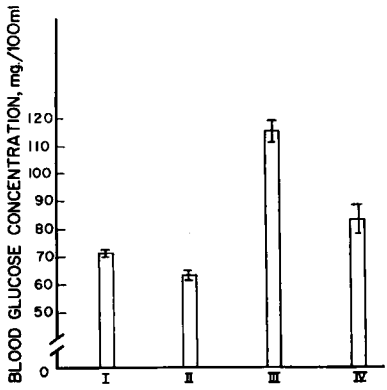

Fig. 3—Effect of MJ-1999 pretreatment on CPZ-induced hyperglycemia. Blood glucose determined 90 min. after CPZ (15 mg./kg.) and 120 min. post-MJ-1999 (10 mg./kg.) pretreatment. Key: I, saline control; II, MJ-1999; III, CPZ; IV, CPZ + MJ-1999. Means from 5 rats.

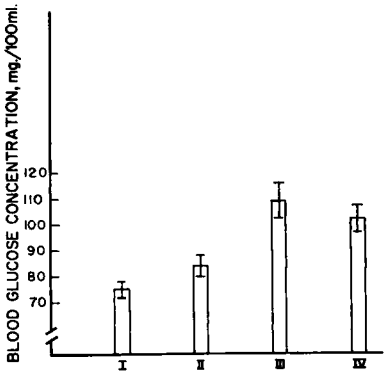

Fig. 4—Effect of phenoxybenzamine (DZ) pretreatment on CPZ-induced hyperglycemia. Blood glucose determined 90 min. after CPZ (15 mg./kg.) and 150 min. post-phenoxybenzamine (10 mg./kg.) injection. Key: I, saline control; II, DZ; III, CPZ; IV, CPZ + DZ. Means from 4 animals.

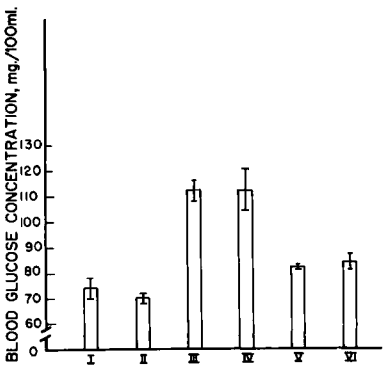

Fig. 5—Inhibition of isoproterenol- and epinephrine-induced hyperglycemia by MJ-1999. MJ-1999 (10 mg./kg., i.p.) administered 30 min. prior to isoproterenol (1 mg./kg.) or epinephrine 30 mcg./kg.). Blood glucose determined 60 min. after MJ-1999. Key: I, saline control; II, MJ-1999; III, Epi.; IV, Isoproterenol; V, Epi. + MJ-1999; VI, Isoproterenol + MJ-1999. Means from 4 animals.

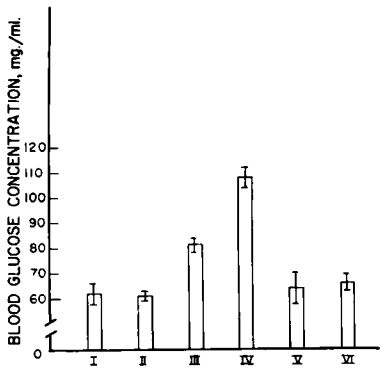

Fig. 6—Effect of MJ-1999 on CPZ potentiation of epinephrine-induced hyperglycemia in adrenalectomized rats. Epinephrine HCl (30 mcg./kg.) injected 60 min. after CPZ (15 mg./kg.) and MJ-1999 injected 30 min. prior to CPZ. Blood glucose determined 30 min. after epinephrine. Key: I, saline control; II, CPZ; III, Epi.; IV, Epi. + CPZ; V, Epi. + MJ-1999; VI, Epi. + CPZ + MJ-1999. Means from 5 animals.

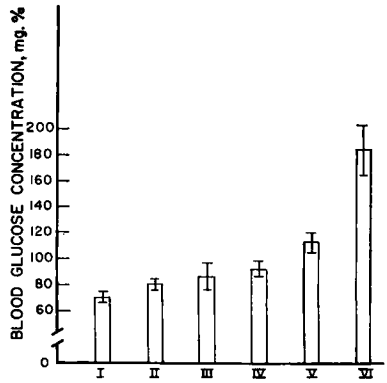

Fig. 8—Effect of phenoxybenzamine (DZ) and chlorpromazine (CPZ) on glucose load in intact rats. CPZ (15 mg./kg.) and DZ (10 mg./kg.) administered 60 min. prior to glucose loading and blood glucose determined 2 hr. after loading. Key: I, saline control; II, DZ; III, CPZ; IV, glucose; V, Glucose + DZ; VI, Glucose + CPZ. Means from 4 animals. Glucose load 2 g./kg., i.p.

sponses were blocked by MJ-1999 in both intact and adrenalectomized rats.

Effect of Chlorpromazine and Phenoxybenzamine on Glucose Tolerance—The hyperglycemia following glucose loading was significantly increased ($p < 0.001$ at 2-hr. interval) in chlorpromazine-treated adrenalectomized (Fig. 7) and intact (Fig. 8) rats ($p < 0.001$). This decreased tolerance to glucose load may indicate impairment of peripheral glucose utilization by chlorpromazine. Since phenoxybenzamine had also potentiated epinephrine-induced hyperglycemia it was of interest to observe its influence on glucose tolerance. As shown in Fig. 8, tolerance to glucose loading was not altered by phenoxybenzamine.

DISCUSSION

Although the blood pressure rise induced by epinephrine can be blocked by chlorpromazine (1, 5), contradictory observations have been made with respect to the glycemic action of epinephrine and chlorpromazine. Gupta *et al.* (5) found that chlorpromazine-induced hyperglycemia was enhanced by epinephrine in rabbits, but Courvoisier *et al.* (1) found no effect of chlorpromazine on epinephrine-induced hyperglycemia. However, this study in rats indicates a definite potentiation of epinephrine hyperglycemia by chlorpromazine pretreatment. From these studies it may be concluded that in the rat the responsible receptors for blood pressure and hyperglycemia affected by epinephrine are not identical. It appears that in the rat the β-adrenergic receptors are involved in the hyperglycemic action since it can be blocked by a β-adrenergic-blocking agent such as MJ-1999 and not by phenoxybenzamine (α-adrenergic-blocking agent). Epinephrine-induced hyperglycemia was markedly potentiated by phenoxybenzamine pretreatment. This potentiation probably resulted from the blockade of α-adrenergic receptors by phenoxybenzamine which increases the effect of epinephrine on the β-adrenergic receptors. This is analogous to the well known "epinephrine reversal" phenomenon in regard to blood pressure responses after α-receptor blockade. Like phenoxybenzamine, the chlorpromazine potentiation of epinephrine-induced hyperglycemia may also be explained, in part, on the basis of the "epinephrine reversal" phenomenon. It has been shown in this study and by others (11) that chlorpromazine pretreatment reduces the tolerance to glucose loading in rats. It would appear that chlorpromazine potentiation of epinephrine-induced hyperglycemia is probably the result of a twofold action, (*a*) the impairment of peripheral utilization of glucose, and (*b*) the production of α-adrenergic blockade.

Although it appears that several mechanisms are involved in the glycemic action of chlorpromazine, the present data indicate that the primary mechanism by which chlorpromazine induces hyperglycemia is through the release of epinephrine. The chlorpromazine potentiation of epinephrine-induced hyperglycemia is independent of the adrenal glands and may be considered a secondary mechanism.

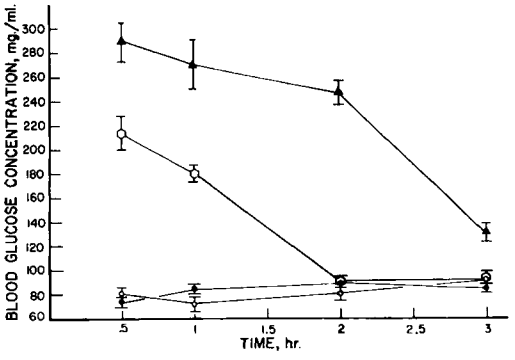

Fig. 7—Effect of chlorpromazine on glucose load in fasted adrenalectomized rats. CPZ (15 mg./kg., i.p.) administered 60 min. before glucose loading (2 g./kg., i.p.). Key: ○, CPZ alone; ○, glucose alone; ▲, CPZ + glucose; ●, saline control. Means from 4 rats.

REFERENCES

(1) Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M., and Koetschet, P., *Arch. Intern. Pharmacodyn.*, **92**, 305(1953).
(2) Norman, D., and Hiestand, W. A., *Proc. Soc. Exptl. Biol.*, **90**, 89(1955).
(3) Simoes, M. S., and Osswald, W., *Metabolism*, **4**, 333 (1955).
(4) Ryall, R. W., *Brit. J. Pharmacol.*, **11**, 339(1956).
(5) Gupta, S. K., Patel, M. A., and Joseph, A. D., *Arch. Intern. Pharmacodyn.*, **128**, 82(1960).
(6) LeBlanc, J. A., *Proc. Soc. Exptl. Biol. Med.*, **103**, 621 (1960).
(7) Bonaccorsi, A., Garattini, S., and Jori, A., *Brit. J. Pharmacol.*, **23**, 93(1964).
(8) Jori, A., and Carrara, M. C., *J. Pharm. Pharmacol.*, **18**, (9), 623(1966).
(9) Hiles, B. W., *J. Am. Med. Assoc.*, **162**, 1651(1956).
(10) CooperBerg, A. A., and Eidlow, S., *Can. Med. Assoc. J.*, **75**, 746(1956).
(11) Jori, A., Bernardi, D., and Garattini, S., *Int. J. Neuropharmacol.*, **3**, 553(1964).
(12) Antonis, A., Clark, M. L., Molony, M., Hodge, R. L., and Pilkington, T. R. E., *Lancet*, **1**, 1135(1967).

Keyphrases

Hyperglycemic mechanism—chlorpromazine, epinephrine
Chlorpromazine potentiation—epinephrine hyperglycemia
β-Adrenergic receptors—relation to hyperglycemia

Potential Antineoplastic Agents: *N*-(2-Benzoxazolyl)amino Acid Esters

By SHYAM B. ADVANI* and JOSEPH SAM

The investigation of the preparation of *N*-(2-benzoxazolyl)aminoacids and esters from the reaction of aminoacids and esters with either 2-chlorobenzoxazole or 2-benzoxazolinone is described.

TUMORS, because of their parasitic nature, depend upon the host for nutrition and growth. Moreover, because of a limited blood supply, tumor cells depend solely on highly effective transport mechanisms for nutrients. Transport mechanisms involving the accumulation of aminoacids in tumor cells have been studied extensively (1). Tumor cells, being more dependent than the normal tissues on the surrounding fluids for an adequate supply of amino acids, are susceptible to attack by substances which interfere with amino acid transport. Ethionine not only was found to concentrate to a greater extent in tumor cells than methionine, but also was found to possess antineoplastic activity (2). Cycloleucine (1-aminocyclopentanecarboxylic acid) was reported to inhibit growth of tumors by inhibiting transport of other amino acids (3–5). Nitrogen mustards of phenylalanine were found to possess high antitumor activity, probably because of increased transport to the tumor cells (6).

The marked antineoplastic activity of some amino acids prompted the preparation of *N*-(2-benzoxazolyl)amino acids and esters (III, Table I) from 2-chlorobenzoxazole (I) and aminoacids or ethyl esters of aminoacids (II). No reaction was observed when 2-chlorobenzoxazole (I) was treated with either tyrosine or leucine in dry ethanol or benzene according to the method of Montgomery (7). Glycine, on the other hand, gave the desired product (III*c*). The esterification of III*c* in ethanol gave ethyl *N*-(2-benzoxazolyl)glycinate (III*b*). When phenylalanine in ethanol was treated with I in the presence of triethylamine, the ester (III*d*) rather than the acid was isolated. Whereas most amino acids did not react with I, the esters of the amino acids gave satisfactory results. When dimethylformamide (DMF) was used as a solvent in the reactions above, 2-dimethylaminobenzoxazole was isolated as a product (8).

The condensation of I with ethyl *p*-aminobenzoate gave ethyl *N*-(2-benzoxazolyl)-*p*-aminobenzoate (III*h*). The corresponding acid (III*i*) was obtained either from the sodium hydroxide hydrolysis of III*h* or from the reaction of I with

Received May 22, 1968, from the Department of Pharmaceutical Chemistry, School of Pharmacy, University of Mississippi, University, MS 38677
Accepted for publication June 27, 1968.
Presented to the Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, Miami Beach meeting, May 1968.
Abstracted in part from a thesis submitted by S. B. Advani to the Graduate School, University of Mississippi, in partial fulfillment of Doctor of Philosophy degree requirements.
This investigation was supported by grant CA 07857 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.
* Present address: Pennsalt Chemical Corporation, King of Prussia, Pennsylvania.