Brit. J. Pharmacol. (1964), 23, 93–100.

STUDIES ON THE HYPERGLYCAEMIA INDUCED BY CHLORPROMAZINE IN RATS

BY

A. BONACCORSI, S. GARATTINI AND A. JORI

From the Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea, 62, Milano, Italy

(*Received December* 16, 1963)

Chlorpromazine induces in rats a marked and long-lasting hyperglycaemia which (*a*) is more marked at low than high room temperatures, (*b*) is inhibited by phentolamine but not by dibenamine, and (c) is prevented by adrenalectomy, by removal of the adrenal medullae and by treatment of the rats with reserpine. Other experimental results suggest that there is a correlation between the hyperglycaemia and the hypothermia induced by chlorpromazine and by its congeners. The hyperglycaemia seems to be the result of at least two factors: an activation of the adrenergic mechanisms and an impaired peripheral utilization of glucose.

Chlorpromazine interferes with carbohydrate metabolism. In the early observations of Courvoisier, Fournel, Ducrot, Kolsky & Koetscher (1953) chlorpromazine was considered to be a hyperglycaemic agent. An increase in blood glucose levels after administration of chlorpromazine has been observed in mice (Norman & Hiestand, 1955), hamsters (Norman & Hiestand, 1955), rats (Le Blanc, 1960; Soulairac, Soulairac & van Steenkiste, 1961), rabbits (Gupta, Patel & Joseph, 1960) and dogs (Simoes & Oswald, 1955). Other investigators, however, did not find any significant effect on blood sugar in rats (Norman & Hiestand, 1955) and in rabbits (Ryal, 1956) after chlorpromazine administration. Furthermore, chlorpromazine does not affect the hyperglycaemia induced by adrenaline (Courvoisier *et al.*, 1953; Delga & Hazard, 1957; Gupta *et al.*, 1960) to any marked extent although the hypertensive response is inhibited (Delga & Hazard, 1957; Gupta *et al.*, 1960).

Contradictory conclusions have also been reached on the relationship between chlorpromazine and insulin and alloxan. For instance Lindaur (1956) and Norman & Hiestand (1955) demonstrated antagonism between chlorpromazine and insulin, but other investigators did not reach the same conclusion (Lancaster & Jones, 1954; Christy, Longson, Horwitz & Knight, 1957; Le Blanc, 1960; Soulairac, 1961). In mice chlorpromazine increases the severity of diabetes due to alloxan (Norman & Hiestand, 1955), but in dogs it protects against this effect (Simoes & Oswald, 1955).

The interest in this problem is not merely academic, since hyperglycaemia occurs in humans during therapy with chlorpromazine (Lancaster & Jones, 1954; Hüdepohl & Lederbogen, 1963) and controlled diabetic patients become unstable (Hiles, 1956).

These results suggested an investigation of the changes in blood glucose levels after treatment of rats with chlorpromazine. It was hoped to obtain additional knowledge of the mechanisms by which chlorpromazine and related compounds alter carbohydrate metabolism *in vivo*.

METHODS

Female Sprague-Dawley rats of an average weight of 150 g were used. Chlorpromazine was usually injected intraperitoneally in a dose of 15 mg/kg. Removal of the adrenal medullae was performed according to Evans (1936). Blood glucose determinations were carried out on blood obtained from the carotid artery or from the tail (Nelson, 1944) after 16 hr of fasting. Rectal body temperature was recorded with an electric thermometer. Blood concentrations of chlorpromazine up to 1 mg/ml. did not interfere with the determination of glucose.

Drugs used were: chlorpromazine (Largactil, Farmitalia), perphenazine (Trilafon, Schering), trifluprομazine (Vesprin, Squibb), thioridazine (Melleril, Sandoz), phentolamine (Regitin, Ciba), reserpine (Serpasil, Ciba) and dibenamine.

RESULTS

Figs. 1 and 2 show the effect of chlorpromazine on blood glucose concentrations in rats. The hyperglycaemia is clearly shown by both the dose-effect and the time-effect relationships. These curves demonstrate that the minimal effective dose is 10 mg/kg and that 15 mg/kg of chlorpromazine raises the blood sugar for at least 6 hr.

To investigate the causes of the hyperglycaemia induced by chlorpromazine various approaches have been followed.

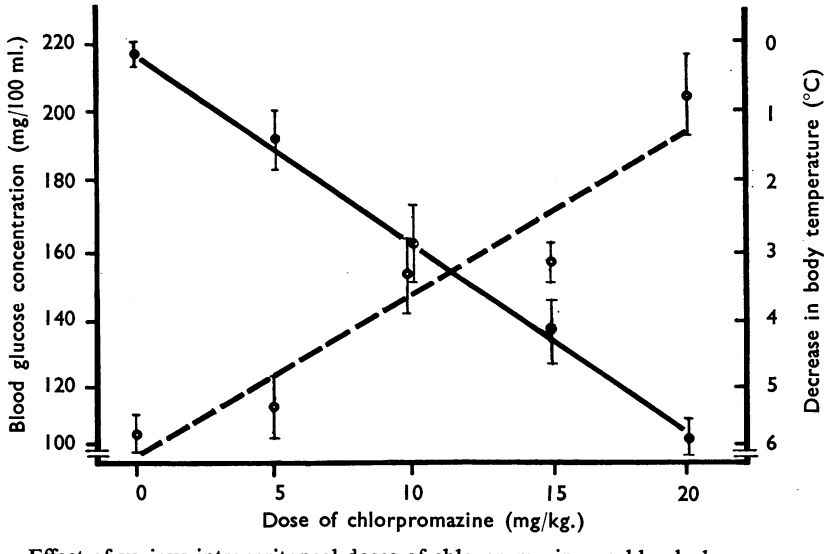

Fig. 1. Effect of various intraperitoneal doses of chlorpromazine on blood glucose concentration (○ - - - ○) and body temperature (● —— ●) 1 hr after treatment. The vertical bars represent standard errors. Each pair of results represents the average from twelve rats.

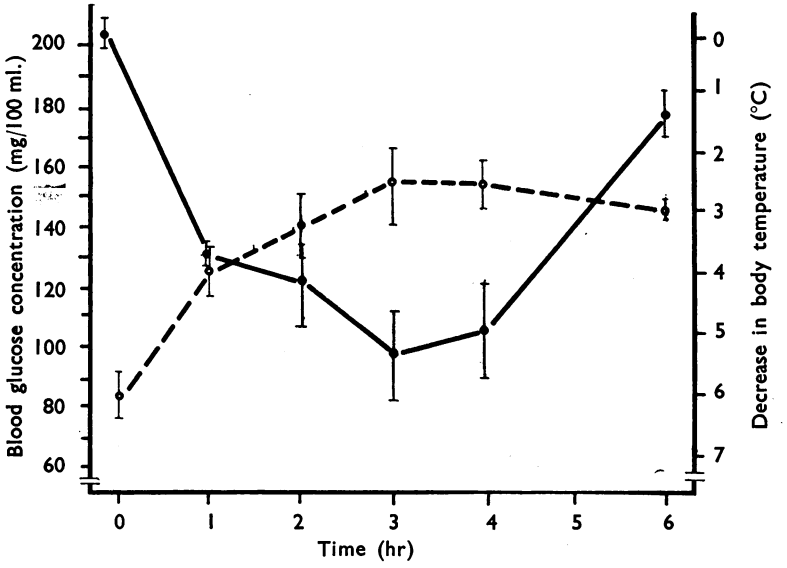

Fig. 2. Effect of chlorpromazine (15 mg/kg, intraperitoneally) on blood glucose concentration (○ - - - ○) and body temperature (● —— ●). The vertical bars represent standard errors. Each pair of results represents the average from eight rats.

Effect of room temperature on hyperglycaemia induced by chlorpromazine. Since it is known that the toxicity of chlorpromazine varies greatly at different environmental temperatures (Berti & Cima, 1954; Binet & Decaud, 1960) the effect of chlorpromazine on blood glucose was evaluated at room temperatures of 4°, 18° and 35° C. The results are shown in Table 1. The extent of hyperglycaemia produced by chlorpromazine increases with the lowering of room temperatures and with the degree of hypothermia produced.

TABLE 1

EFFECT OF CHLORPROMAZINE ON BLOOD GLUCOSE CONCENTRATIONS AT VARIOUS ROOM TEMPERATURES

Values are means (of at least ten determinations) and standard errors. Chlorpromazine (15 mg/kg) was injected intraperitoneally, and blood glucose concentrations determined 1 hr later. Significance of the differences between groups : 1–3, $P < 0{\cdot}01$; 1–2, $P < 0{\cdot}05$; and 2–3, $P > 0{\cdot}05$

Group	Room temperature (°C)	Body temperature (°C)	Blood glucose (% change)
1	4	28·9±0·3	+104±12
2	18	33·2±0·5	+ 81±14
3	35	35·4±0·2	+ 63± 7

Disappearance of glucose from the blood stream. The hypothermia induced by chlorpromazine could explain the increase in blood glucose concentration as due to impaired utilization. The hyperglycaemia following glucose loading is much more pronounced in chlorpromazine- than in saline-treated rats (Table 2). These results support the view that chlorpromazine may, at least in part, act as an hyperglycaemic agent by preventing utilization of glucose.

TABLE 2

DISAPPEARANCE OF GLUCOSE FROM BLOOD STREAM

Chlorpromazine was given 30 min before glucose. The glucose was dissolved in water at the concentration of 200 mg/ml. Injections were intraperitoneal. Blood glucose values are means with standard errors

No. of rats	Treatment	Dose (mg/kg)	Blood glucose (mg/100 ml.) after 0·5 hr	1 hr	2 hr
15	Saline	—	—	91± 2	—
10	Saline +glucose	2,000	131± 2	100± 4	118± 6
5	Chlorpromazine	5	106± 3	103± 3	107± 6
10	Chlorpromazine +glucose	2,000	233±17	141±18	145±13

Effect on adrenergic activity. Chlorpromazine might produce hyperglycaemia by increasing catechol amine activity. This hypothesis has been preliminarily tested by observing the effect of two adrenolytic agents on the rise in blood sugar after treatment with chlorpromazine. Phentolamine, but not dibenamine, reduced the hyperglycaemia (Table 3). These results are particularly significant when it is considered that hyperglycaemia due to adrenaline is inhibited by phentolamine but not by dibenamine (Ellis, Beckett & Boutwell, 1957). The importance of the adrenergic mechanism is also supported by the results obtained in rats treated with

TABLE 3

EFFECT OF ADRENERGIC BLOCKING AGENTS ON THE HYPERGLYCAEMIA INDUCED BY CHLORPROMAZINE

Phentolamine and dibenamine were given 1 hr after chlorpromazine. Determinations were carried out 2 hr after chlorpromazine administration. Injections were intraperitoneal. Blood glucose values are means with standard errors

No. of rats	Treatment	Dose (mg/kg)	Blood glucose (mg/100ml)
10	Saline	—	81± 2
15	Chlorpromazine	15	142± 7
10	Phentolamine	5	85± 3
10	Chlorpromazine +phentolamine	15 +5	109± 7
5	Dibenamine	10	117± 5
5	Dibenamine	20	111± 7
5	Chlorpromazine +dibenamine	15 +10	141±21
5	Chlorpromazine +dibenamine	15 +20	160±15

reserpine. The depletion of tissue catechol amines by reserpine partly prevents the hyperglycaemic effect of chlorpromazine. However, this effect could be related to a decreased absorption of chlorpromazine due to the hypothermia exhibited by rats treated with reserpine (Table 4).

Effect in rats with adrenal glands or medullae removed. From Table 5 it is evident that adrenalectomy and removal of the adrenal medullae considerably reduce the hyperglycaemia due to chlorpromazine. Neither operation affected the hyperglycaemic response to adrenaline.

TABLE 4

EFFECT OF CHLORPROMAZINE IN RESERPINIZED RATS

Reserpine was given 16 hr before chlorpromazine. Determinations were carried out 2 hr after chlorpromazine. Injections were intraperitoneal, Values are means with standard errors

No. of rats	Treatment	Dose (mg/kg)	Body temperature (°C)	Blood glucose (mg/100ml.)
5	Saline	—	36·0±0·4	69± 4
10	Reserpine	5	31·8±0·9	131± 5
10	Reserpine +chlorpromazine	5 +15	32·8±1	139± 6
10	Chlorpromazine	15	28·3±0·6	192±13

Relationship between hypothermia and hyperglycaemia. In Fig. 3 the effect of chlorpromazine on blood glucose concentration is plotted against the effect on body temperature. It is evident that there is a good correlation which is linear and may be expressed by the equation $y = -3.73 + 15.53\ x$ (y = increase in blood glucose; x = decrease in body temperature). The curved lines show the confidence limits of linear regression.

TABLE 5

BLOOD GLUCOSE CONCENTRATIONS (mg % ± S.E.) IN INTACT, "DEMEDULLATED" AND ADRENALECTOMIZED RATS AFTER CHLORPROMAZINE AND ADRENALINE

Determinations were carried out 90 min after treatments. The analysis of variance shows that there is no interaction between "operations" and adrenaline (100 μg/kg, subcutaneously), a significant interaction ($P < 0.01$) has been found between "operations" and chlorpromazine (15 mg/kg, intraperitoneally). Blood glucose values are means with standard errors

	Blood glucose (mg/100 ml.) in rats		
Treatment	Intact	Demedullated	Adrenalectomized
Solvents	84± 4	89±10	92± 4
Chlorpromazine	144±19	96± 8	108±10
Adrenaline	133± 4	148±12	138± 8

Three chlorpromazine congeners have been tried in similar experimental conditions. The results (Table 6) show that there is also a good correlation between hypothermia and hyperglycaemia with these phenothiazines. The four regression lines are statistically parallel.

TABLE 6

RELATIONSHIP BETWEEN HYPERGLYCAEMIA AND HYPOTHERMIA AFTER PHENOTHIAZINES

The linear regressions of all phenothiazines listed are statistically parallel. Injections were intraperitoneal. Values are means with standard errors

No. of rats	Treatment	Dose (mg/kg)	Body temperature (°C)	Blood glucose (mg/100 ml.)	Coefficient of regression (by/x)
48	Chlorpromazine	15	30·1±0·32	191± 8·6	15·53
20	Trifluprομazine	30	30·1±0·52	227±11	13·97
20	Perphenazine	15	31·6±0·5	206±18	22·50
20	Thioridazine	30	31·0±0·8	184±11	29·46
10	Saline	—	35·9±0·5	105±4	—

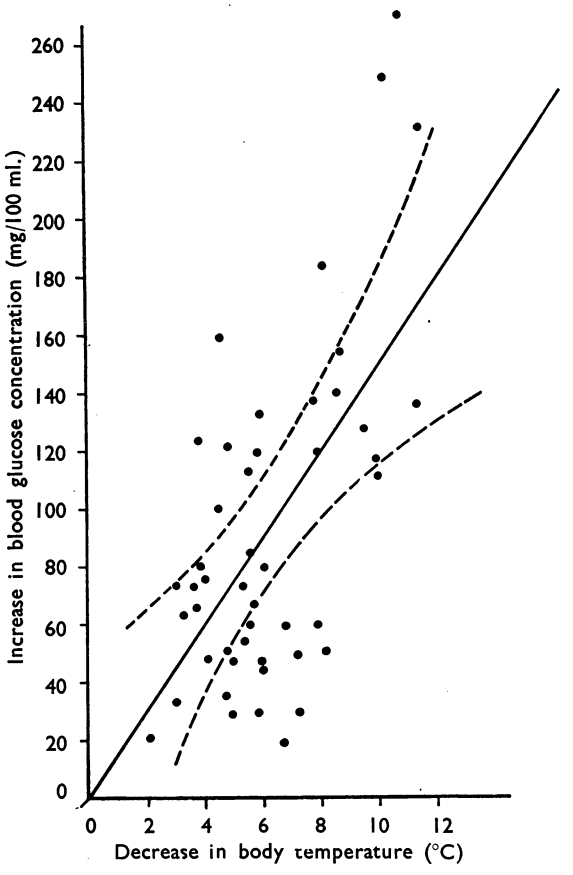

Fig. 3. Correlation between increase in blood glucose concentration and decrease in body temperature after treatment wtih chlorpromazine (15 mg/kg, intraperitoneally). Each point represents a result from one animal. The continuous line is the regression line, $y = 3{\cdot}73 + 15{\cdot}53\,x$.

DISCUSSION

Chlorpromazine induces a sustained hyperglycaemia in rats. In this investigation it has been shown that there are at least two mechanisms responsible for the increase in blood glucose concentration after treatment with chlorpromazine. Loading with glucose results in a more marked hyperglycaemia in rats treated with chlorpromazine than in controls (Table 2), and this suggests that chlorpromazine decreases peripheral utilization of glucose. On the other hand chlorpromazine seems to interfere with catechol amine activity. Indirect support for this second mechanism is obtained from (*a*) the inhibition of hyperglycaemia due to chlorpromazine by the adrenolytic agent phentolamine (Table 3), (*b*) the results of removal of the adrenal glands or medullae (Table 5) and (*c*) the result of depletion of catechol amines as produced by reserpine (Table 4). No experimental data, however, support the hypothesis that chlorpromazine acts as an hyperglycaemic agent by releasing catechol amines

from the adrenal glands (Camanni, Molinatti & Olivetti, 1959) or from other tissues (Gey & Pletscher, 1961). It has instead been reported that chlorpromazine impairs the uptake of catechol amines (Axelrod, Whitby & Hertting, 1961; Axelrod, Hertting & Potter, 1962).

Indeed there is a correlation between hypothermia and hyperglycaemia as shown by studies with chlorpromazine and three other centrally acting phenothiazines. These results favour the hypothesis that the hypothermia induced by chlorpromazine is responsible for the hyperglycaemia through an impaired utilization and an increased mobilization of glucose. These conclusions do not exclude other explanations such as a direct effect of chlorpromazine on enzymes relevant to carbohydrate metabolism (Moraczewski & du Bois, 1959) or an effect on cell permeability to glucose.

The help given by Miss D. Bernardi is gratefully acknowledged.

REFERENCES

AXELROD, J., HERTTING, G. & POTTER, L. (1962). Effect of drugs on the uptake and release of ^{3}H-norepinephrine in the rat heart. *Nature (Lond.)*, **194**, 297.

AXELROD, J., WHITBY, L. G. & HERTTING, G. (1961). Effect of psychotropic drugs on the uptake of H_3-norepinephrine by tissues. *Science*, **133**, 383–384.

BERTI, T. & CIMA, L. (1954). Influenza della temperatura sull'azione farmacologica della cloropromazina. *Arch. ital. Sci. farmacol.*, **4**, 273–274.

BINET, P. & DECAUD, J. (1960). Influence de la température ambiante sur la température rectale du rat traité par quelques dérivés de la phénothiazine. *Thérapie*, **15**, 253–257.

CAMANNI, F., MOLINATTI, G. M. & OLIVETTI, M. (1959). Abolition by chlorpromazine of the inhibiting effect of iproniazid on the depletion of adrenal catchol amines induced by reserpine. *Nature (Lond.)*, **184**, 65–66.

CHRISTY, N. P., LONGSON. D., HORWITZ, W. A. & KNIGHT, M. M. (1957). Inhibitory effect of chlorpromazine upon the adrenal cortical response to insulin hypoglycemia in man. *J. clin. Invest.*, **36**, 543–549.

COURVOISIER, S., FOURNEL, J., DUCROT, A., KOLSKY, M. & KOETSCHER, P. (1953). Propriétés pharmacodynamiques du chlorhydrate de chloro-3(diméthylamino-3'propyl)-10 phénothiazine (4,560 R.P.). *Arch. int. Pharmacodyn.* **92**, 305–361.

DELGA, J. & HAZARD, R. (1957). Action de la chloropromazine sur quelques actions de l'adrenaline et de la noradrenaline chez le chien. *Arch. int. Pharmacodyn.* **109**, 446–456.

ELLIS, S., BECKETT, S. B. & BOUTWELL, J. H. (1957). Dibenamine blockade of epinephrine and glucagon hyperkalemias. *Proc. Soc. exp. Biol. (N.Y.)*, **94**, 343–345.

EVANS, G. (1936). Adrenal cortex and endogenous carbohydrate formation. *Amer. J. Physiol.*, **114**, 297–308.

GEY, K. F. & PLETSCHER, A. (1961). Influence of chlorpromazine and chlorprothixene on the cerebral metabolism of 5-hydroxytryptamine, norepinephrine and dopamine. *J. Pharmacol. exp. Ther.*, **133**, 18–24.

GUPTA, S. K., PATEL, M. A. & JOSEPH, A. D. (1960). Effect of chlorpromazine and epinephrine on blood sugar of rabbits. *Arch. int. Pharmacodyn.*, **128**, 82–88.

HILES, B. W. (1956). Hyperglycemia and glycosuria following chlorpromazine therapy. *J. Amer. med. Ass.*, **162**, 1651.

HÜDEPOHL, M. & LEDERBOGEN, K. (1963). Hemmung der hypoglykämischen Wirkung des Rastinon beim Menschen durch megaphen und ihre Aufhebung durch Pendiomid. *Klin. Wschr.*, **41**, 245–246.

LANCASTER, N. P. & JONES, D. H. (1954). Chlorpromazine and insulin in psychiatry. *Brit. med. J.* **ii**, 565–567.

LE BLANC, J. A. (1960). Potentiation of chlorpromazine by insulin. *Proc. Soc. exp. Biol. (N.Y.)*, **103**, 621–623.

LINDAUR, V. (1956). Zur Frage des Einflusses von Chloropromacin auf den Blutzucker. *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.*, **229**, 253–257.

MORACZEWSKI, A. S. & DU BOIS, K. P. (1959). The influence of chlorpromazine on intermediary carbohydrate metabolism. *Arch. int. Pharmacodyn*, **120**, 201–221.

NELSON, N. (1944). A photometric adaptation of the Somogyi method for the determination of glucose. *J. biol. Chem.*, **153**, 375–380.

NORMAN, D. & HIESTAND, W. A. (1955). Glycemic eflects of chlorpromazine in the mouse, hamster and rat. *Proc. Soc. exp. Biol. (N.Y.)*, **90**, 89–91.

RYAL, R. W. (1956). Some actions of chlorpromazine. *Brit. J. Pharmacol.*, **11**, 339–345.

SIMOES, M. S. & OSWALD, W., (1955). Chlorpromazine protection against alloxan diabetes. *Metabolism*, **4**, 333–336.

SOULAIRAC, A., SOULAIRAC, M. L. & VAN STEENKISTE, J. N. (1961). Action of chlorpromazine, amphetamine and iproniazid on insulin hypoglycemia in the rat. *Ann. Endocr. (Paris)*, **22**, 367–372.