Effect of Hypothermia on the Chlorpromazine-Induced Bradycardia and Hypotension in the Rat

By K. F. FINGER, R. L. CAVANAGH, and E. E. MOOG

The administration of chlorpromazine (0.5 mg./Kg.) caused a rapid fall in blood pressure and a decreased heart rate in rats. A significant potentiation in both the extent and the duration of the heart rate effects was observed in hypothermic animals as compared to normothermic animals. No significant differences were observed in the blood pressure effects during the period of observation. It was also established that fatty acid mobilization, reflexly induced by chlorpromazine's hypotensive action, was inhibited in hypothermic animals but not in normothermic animals. These data suggest that chlorpromazine more effectively inhibits adrenergic mechanisms in the hypothermic animal and this mechanism may explain the potentiation of heart rate effects observed in this study.

CHLORPROMAZINE exerts a variety of pharmacological actions in both man and laboratory animals. Included among these are antiadrenergic, antihistaminic, and anticholinergic effects and its characteristic central nervous system depression (1). These actions manifest themselves as a decrease in spontaneous motor activity, altered behavioral patterns (primarily in response to external environmental factors), hypothermia, hypotension, and alterations in heart rate (1–3). Interest centered around the effects of chlorpromazine on blood pressure and heart rate with particular reference to the quantitative aspects of its antiadrenergic actions. During the course of preliminary investigations, it was noted that in regard to its effects on heart rate, chlorpromazine appeared to exert a prolonged action in hypothermic animals as compared to those which were maintained normothermic. The investigations into the possible reasons for these differences is the subject of this report.

EXPERIMENTAL

Methods.—Male Sprague-Dawley rats, weighing between 350 and 400 Gm., were employed in this study. They were anesthetized with urethan (approximately 1.0 Gm./Kg. i.p.), their femoral and carotid vessels cannulated for purposes of drug administration and blood pressure and heart rate recording, respectively, and either maintained normothermic by the use of a warming element or allowed to become hypothermic by omitting the warming procedure. Rectal temperatures were monitored for all animals utilizing the Yellow Springs Instrument Co. Telethermometer. Blood pressures and heart rates were determined from tracings obtained with the E and M Physiograph equipped with a Statham P23 transducer.

Control periods of sufficient length to assure a stabilized blood pressure and heart rate were continuously recorded prior to drug administration. Chlorpromazine, 0.5 mg./Kg., was administered i.v. in a volume of 0.1 ml./Kg. and control animals received 0.1 ml./Kg. of saline. Blood pressures and heart rates were monitored continuously for 20 min. immediately following drug administration and thereafter for several minutes at 20-min. intervals for approximately 3 hr. At least six animals were employed in each group and the data to be presented here are expressed as the mean value obtained ± the standard error of the mean.

For the determination of nonesterified fatty acids in plasma, the animals were treated in the manner described above for the cardiovascular experiments except that blood samples were withdrawn *via* the carotid cannula and the plasma assayed for fatty acids by a modification of the method of Dole (4).

RESULTS AND DISCUSSION

Body Temperature Changes.—The changes in body temperature produced by drug treatment and the experimental procedures are shown in Fig. 1. These results show that the procedures employed produced a highly significant difference in rectal temperature between those animals maintained with a warming element and those which were not provided with an external heat source. It is apparent from this figure that the use of the warming element maintained body temperature at a reasonably constant value, while those animals which were not heated became hypothermic. Chlorpromazine, at the low dosage employed in this study, produced an observable but relatively small reduction in rectal temperature.

Effect of Chlorpromazine on Blood Pressure.—The intravenous administration of 0.5 mg./Kg. of chlorpromazine produced a rapid fall in both systolic and diastolic pressure. In Fig. 2, the per cent of initial mean blood pressure has been plotted and the rapid decrease in blood pressure is evident. This hypotensive phase of chlorpromazine's actions was

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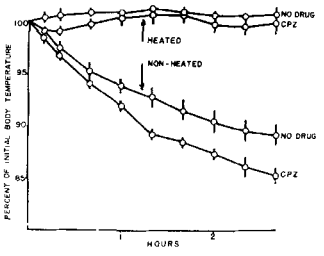

Fig. 1.—Rectal temperatures of rats. Arrows indicate temperature data curves for groups of rats, the upper two curves representing groups maintained with a warming element and the lower two curves those which were not heated.

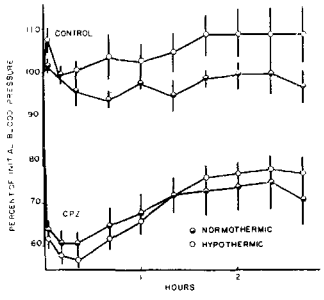

Fig. 2.—Effect of chlorpromazine on blood pressure of hypothermic and normothermic rats.

maintained throughout the period of experimental observation, although a moderate rise was observed to occur between 40 and 80 min. It is also apparent from Fig. 2 that the procedures themselves produced only minor alterations in blood pressure as can be seen in the control curves. It is interesting to note that the hypothermic control group showed slightly higher pressures than did the normothermic group, a result to be anticipated as a result of the induced hypothermia.

Effect of Chlorpromazine on Heart Rate.—Following the administration of chlorpromazine, a lag time occurred before the effects of chlorpromazine became evident on the heart rate. The lag time varied between 2 and 5 min. Following this brief lag period, the heart rate was slowed to an appreciable extent in both normothermic and hypothermic animals. These data are shown in Fig. 3. Twenty minutes after drug administration, the heart rates of the normothermic animals began to return toward normal values, while those of the hypothermic group decreased to even lower values. Indeed, the minimal value of heart rate in the hypothermic animals was still present 40 min. after drug administration, while the heart rate in the normothermic group had returned to approximately 85% of normal. The slope of the line describing the return toward normal values of the heart rate in the hypothermic group is also slightly less than that observed for the normothermic group. In addition, the mean heart rate of the hypothermic group did not return to control values during the period of observation but appeared to plateau out at approximately 85% of the initial value.

It is also interesting to note that there exists a difference in the time at which potentiation of chlorpromazine's heart rate effects are observed and the time of maximum decrease in body temperature. These data are interpreted to indicate that it is not the body temperature *per se* that is the important factor but rather the physiological events, yet unknown, which result in both a decrease in body temperature and the observed potentiation. It is not unusual for body temperature changes to lag behind other events inasmuch as the decrease in body temperature could be due to at least two factors: (*a*) decreased heat production and (*b*) increased heat loss, both of which would be relatively slow and continuous phenomena.

It is also apparent in Fig. 3 that the heart rate of the normothermic control (no drug) group remained quite stable, while a slight tachycardia was observed in the hypothermic control group.

Effect of Hypothermia and Chlorpromazine Treatment on Mobilization of Fatty Acids.—Two different experimental approaches were followed in an attempt to explain the effect of hypothermia on the chlorpromazine-induced changes in heart rate. They were (*a*) to attempt to explain the observed differences in terms of an altered rate of drug metabolism and (*b*) to attempt to obtain evidence indicating alterations in the ability of the chlorpromazine treated, hypothermic animals to respond to reflex homeostatic mechanisms.

The available analytical procedures were not sufficiently sensitive to quantitate the metabolic transformations of chlorpromazine at the dosage employed in this study (0.5 mg./Kg.). Utilizing higher doses, 10 and 30 mg./Kg., the authors were able to identify and quantitate parent drug, chlorpromazine sulfoxide, desmethyl-chlorpromazine, and its corresponding sulfoxide. Preliminary results indicated that while some differences were apparent in the concentrations of certain metabolites, a significant portion of the metabolized chlorpromazine was not accounted for by the moieties assayed. Furthermore, the rather high dosages employed in this phase of the study may have flooded enzymic systems, thus masking relatively small but significant alterations in metabolic rates. While this work is continuing, definitive statements on the rate of chlorpromazine metabolism in this system cannot be made.

The second experimental approach was based on the experimental finding reported by Costa *et al.* (5) and those of Pletscher *et al.* (6). These workers have shown that the release and/or uptake of biogenic amines is inhibited by chlorpromazine in hypothermic animals, but this effect is negated when the animals are maintained normothermic or heated. Costa and co-workers (5) were able to

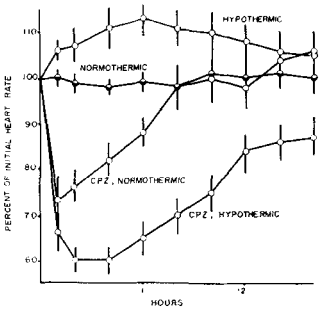

Fig. 3.—Effect of chlorpromazine on heart rate of hypothermic and normothermic rats.

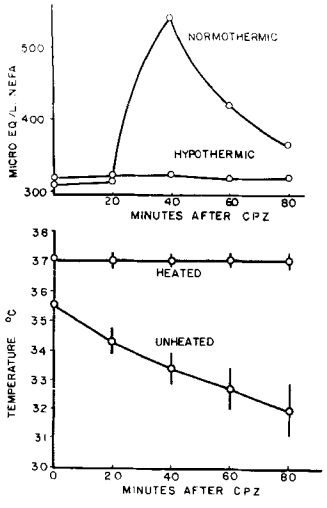

Fig. 4.—Top, effect of hypothermia on fatty acid mobilization in chlorpromazine treated rats. Chlorpromazine dose = 0.5 mg./Kg. i.v. Bottom, rectal temperatures obtained in both heated and unheated chlorpromazine treated rats.

show that chlorpromazine blocked the release of catecholamines by reserpine when the animals were hypothermic but that this action of reserpine was unaffected by chlorpromazine in normothermic animals. Similarly, Pletscher *et al.* (6), studying the uptake of tryptamine as influenced by drugs, found that body temperature had an influence on chlorpromazine's blockade of tryptamine uptake. To ascertain whether a similar effect was operative in this system, an experimental procedure was sought which was (*a*) under the primary control of the sympathetic nervous system and (*b*) sensitive enough to respond to homeostatic, sympathetic mechanisms in the anesthetized animals employed in the present study. Previous work (7–10) had shown that the mobilization of fatty acids from adipose tissue *in vivo* satisfied these criteria. Thus, it was decided to investigate the effect of hypothermia and chlorpromazine treatment on the mobilization of fatty acids *in vivo*.

The results of this phase of the study are shown in Fig. 4. The lower portion of the graph illustrates the changes in body temperature observed in the two groups of animals. Chlorpromazine was administered to both groups of animals at a dose of 0.5 mg./Kg. It is apparent in Fig. 4 that hypothermia effectively antagonized the elevation of plasma fatty acids. These results also show that the dose of chlorpromazine employed was not sufficient to block fatty acid mobilization *per se* inasmuch as significant elevations in plasma fatty acids were obtained in the chlorpromazine treated, normothermic animals. It would appear that an increased sympathetic outflow occurred as a result of the blood pressure lowering effects of the chlorpromazine treated group of animals, probably mediated by the release of catecholamines both locally in adipose tissue and systemically *via* adrenal medullary release. In the hypothermic, chlorpromazine treated animals, however, this manifestation of increased sympathetic tone was antagonized presumably by either inhibiting the release of catecholamines or by a more effective chlorpromazine antagonism of fatty acid mobilization.

It is well known that cold-stressed animals respond by mobilizing fatty acids (9, 10) and the hypothermia *per se* observed in these experiments therefore would have been expected to produce an elevation of nonesterified fatty acids. In contrast to the expected results with hypothermia, chlorpromazine, in sufficient dosage, would have been expected to antagonize fatty acid mobilization (11, 12), yet, in the dose employed, failed to do so in normothermic animals. The combination of chlorpromazine (at a low dose) and hypothermia, however, effectively antagonized fatty acid mobilization.

CONCLUSIONS

It is concluded that the chlorpromazine-induced bradycardia is potentiated by hypothermia with respect to both the extent and the duration of the response. The potentiation may be explained by a reduction in the ability of the hypothermic, chlorpromazine treated animal to respond to reflex homeostatic mechanisms. The antagonism of adrenergic mechanisms implicit in such an explanation may be due to either an effect on the release of adrenergic neurohumoral agents or by a more effective inhibition of adrenergic responses by chlorpromazine in the hypothermic animals.

REFERENCES

(1) Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M., and Koetschet, P., *Arch. Intern. Pharmacodyn.*, **92**, 305 (1953).
(2) Kopera, J., and Armitage, A. K., *Brit. J. Pharmacol.*, **9**, 392(1954).
(3) Finkelstein, M., Spencer, W. A., Hammen, C. S., and Albert, S. N., *Federation Proc.*, **13**, 354(1954).
(4) Finger, K. F., Pereira, J. N., and Schneider, J. A., *Rev. Invest.*, **2**, 41(1962); Finger, K. F., Pereira, J. N., and Schneider, J. A., *Federation Proc.*, **21**, 175(1962).
(5) Costa, E., Gessa, A., and Brodie, B. B., *Life Sciences*, (No. 7) 315(1962).
(6) Pletscher, A., King, E., Staehler, H., and Gey, K. F., *Biochem. Pharmacol.*, **12**, 1065(1963).
(7) Werthiemer, E., and Shapiro, B., *Physiol. Rev.*, **28**, 451 (1958).
(8) Havel, R. J., and Goldfein, A., *J. Lipid Res.*, **1**, 102 (1959).
(9) Salvador, K. A., Colville, K. I., and Burns, J. J., *Ann. N. Y. Acad. Sci.*, **131**, 113(1964).
(10) Gilgen, A., Maickel, R. P., Nikodijevic, O., and Brodie, B. B., *Life Sciences*, (No. 12) 709(1962).
(11) Finger, K. F., Page, J. G., and Feller, D. R., *Biochem. Pharmacol.*, **15**, 1023(1966).
(12) Hulsmann, W. C., Fabius, A. J. M., and de Ruiter H., *Nature*, **202**, 1336(1964).