Brit. J. Pharmacol. (1950), **5**, 195.

THE SITE OF ACTION OF PHENERGAN AND NEOANTERGAN ON BODY TEMPERATURE AND OXYGEN CONSUMPTION IN NORMAL AND ADRENALECTOMIZED RATS

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(Received January 26, 1950)

Recently, Halpern and Briot (1949) have shown that the antihistamine substances, antergan, neoantergan, and phenergan, all cause a fall of body temperature in normal rats and that the effect is much increased after adrenalectomy. Another phenothiazine compound, 3300 R.P., which has little or no antihistamine activity did not have this hypothermic action. The effect of phenergan in a dose of 5 mg./100 g. was increased from an average maximum depression of about 3° C. in normal rats to a maximum of about 10° C. after adrenalectomy. Dutta (1948) has observed a similar effect in mice after injection of several substances including pethidine, atropine, procaine, quinidine, and the antihistamine substance, benadryl. This effect too was much greater after adrenalectomy. Dutta suggested that the action was probably due to the peripheral action of these substances, all of which possess several common properties including that of antagonizing actions of acetylcholine. He concluded that the hypothermic action was probably due to lessened activity, and therefore decreased heat production, in the skeletal muscles owing to this antagonism of acetylcholine. Halpern suggested that the action which he observed in rats with antihistamine substances was more probably due to a central depressant action, with a resultant decrease in basal metabolic rate.

In order to obtain further information on this problem the oxygen consumption of rats was measured before and after injection of suitable doses of phenergan and neoantergan. The temperature changes were also followed. Since adrenalectomized animals were known to be much more sensitive to the hypothermic action, the experiments were repeated in animals after removal of the adrenals.

One group of four animals received an injection of 5 mg. 3300 R.P./100 g. This substance did not have any effect on the rectal temperature in the experiments of Halpern and Briot (1949). Structurally it is closely similar to phenergan, being N-(3′-dimethylamino-2′ : 2′-dimethylpropyl) phenothiazine hydrochloride.

Some incidental observations were also made on the relative sensitivity to these substances of animals which had been kept since birth at a uniform temperature

of 29.5° C. It was found that their hypothermic response differed from that of animals which had been kept at the normally fluctuating animal house temperature.

METHODS

All the rats used were males, aged from 5–6 months. In the early experiments, rats which had been acclimatized for some months to an environmental temperature of 29.5° C. were used ("adapted rats"). Some later experiments were done using rats kept at the usual laboratory temperature until 24 hours before the metabolic rate was measured, when they were placed in a warm room at a constant temperature of 29.5° C.

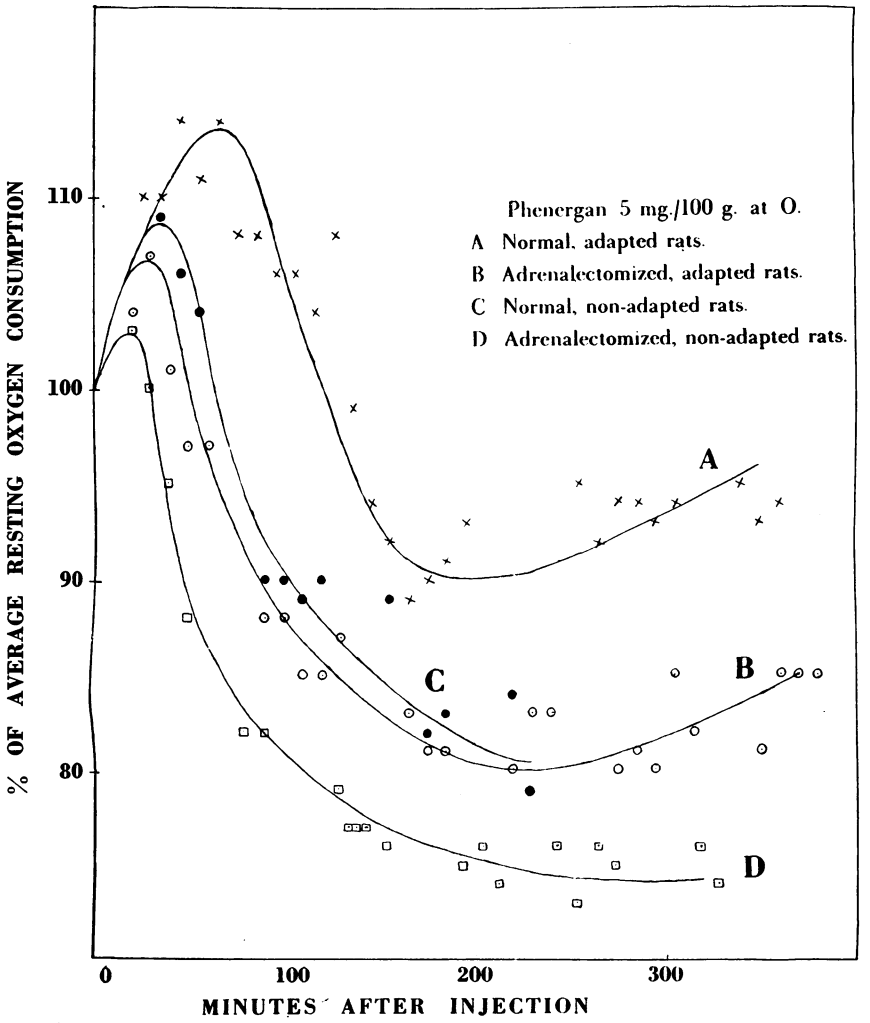

FIG. 1.—Action of phenergan (5 mg./100 g.) on oxygen consumption of adapted and non-adapted rats before and after adrenalectomy. Groups of 5 rats. Abscissae : time in min. after injection. Ordinates: percentage of average oxygen consumption before injection.

(" non-adapted rats "). Oxygen consumption was measured by the method recently described by Bargeton and Krumm-Heller (1948, 1949). By this method, the oxygen consumption of each of five rats is followed at regular intervals. After a series of control observations, the animals were injected with the test substance, replaced in the apparatus, and, after a period of 15 to 30 minutes to allow them to become quiet, determinations were repeated. At intervals of from 30–60 minutes the rectal temperature of each animal was measured by inserting a thermometer through the anus into the sigmoid colon, the readings being made after one minute. For this purpose it was necessary to remove all the animals from the apparatus. This also served the useful purpose of flushing out of the apparatus any toxic gases of intestinal origin expelled by the rats.

Observations of oxygen consumption and of temperature were thus continued for some hours. Actual metabolic rates were not deduced from the results. The average oxygen consumption for the five rats in each period of 5 or 10 minutes was expressed as a percentage of the average value before injection.

The adrenalectomized animals were prepared under ether anaesthesia in the usual way and were used for experiment 72 hours after operation, by which time sensitivity was considerably increased. The cited doses of phenergan (3277 R.P., N-(2′-dimethylamino-*n*-propyl) phenothiazine hydrochloride) are of the base, and those of neoantergan (2786 R.P., N-dimethylaminoethyl-N-*p*-methoxybenzyl-α-aminopyridine) are in terms of its hydrochloride.

RESULTS

Phenergan (Figs. 1 and 2)

In normal, adapted rats the subcutaneous injection of 5 mg. phenergan per 100 g. was followed by an initial increase in the rate of oxygen consumption with a later

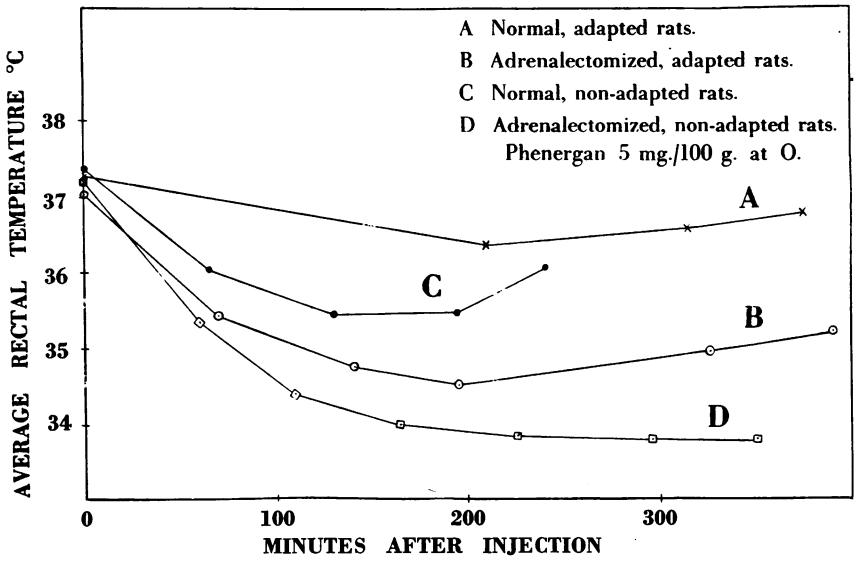

FIG. 2.—Action of phenergan (5 mg./100 g.) on the rectal temperature of " adapted " and " non-adapted " rats before and after adrenalectomy. Abscissae : time in min. after injection. Ordinates: average rectal temperature (1 min.) in °C. Groups of 5 rats.

fall of about 10 per cent at three hours. The average fall in rectal temperature was no more than 1° C. After adrenalectomy, however, the average fall in temperature was 2.5° C. at three hours, and after a slight temporary increase the rate of oxygen consumption fell by about 20 per cent. In another experiment 25 mg. phenergan per 100 g. was injected, and there was only an increase in oxygen consumption during the next four hours, while the temperature, after an initial slight fall, showed a slight increase (Fig. 3). Increased motor activity and even convulsions were seen

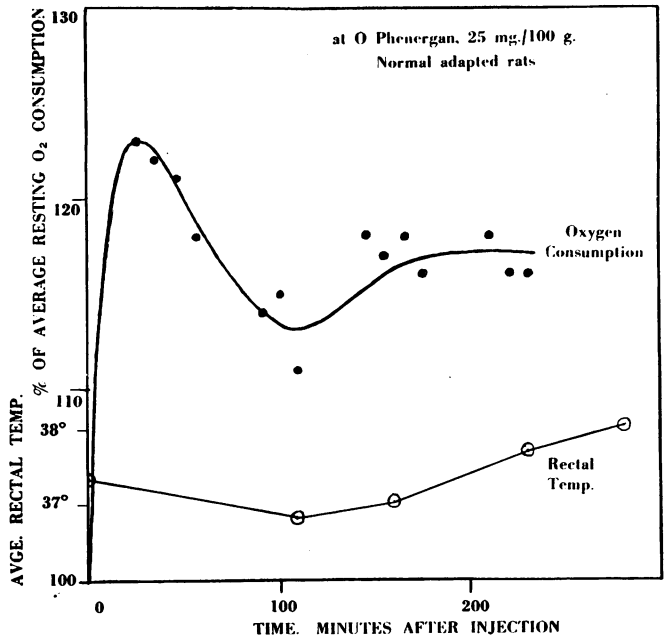

FIG. 3.—Action of a large dose (25 mg./100 g.) of phenergan on oxygen consumption and rectal temperature in a group of 5 rats. Convulsions with increased metabolic activity, but an initial fall in temperature. Abscissae: time. Ordinates: average rectal temperature in °C., and percentage of average O_2 consumption before injection.

in these animals, four of which were dead within 24 hours. In the non-adapted rats, the effects of injection of 5 mg. phenergan per 100 g. were more pronounced than in adapted animals. In the first 90 minutes after injection no increase in oxygen consumption was seen and the temperature fall was greater. These animals were, however, obviously somewhat excited and were not absolutely quiet in the apparatus.

Neoantergan (Figs. 4 and 5)

In normal, adapted rats the dose of 10 mg. neoantergan per kg., which Halpern and Briot had used, was rapidly lethal to four of five animals. All exhibited convulsions, and in those animals from which measurements could be made before death there was a great increase in oxygen consumption. This amounted to 125 and 88 per cent in the two animals which survived for 42 and 49 minutes after injection. In the one animal which did not die there was a sharp rise in the rate of oxygen consumption of about 100 per cent with a return to the normal level after two and a half hours. This animal showed a fall in temperature of 0.8° C. at three hours.

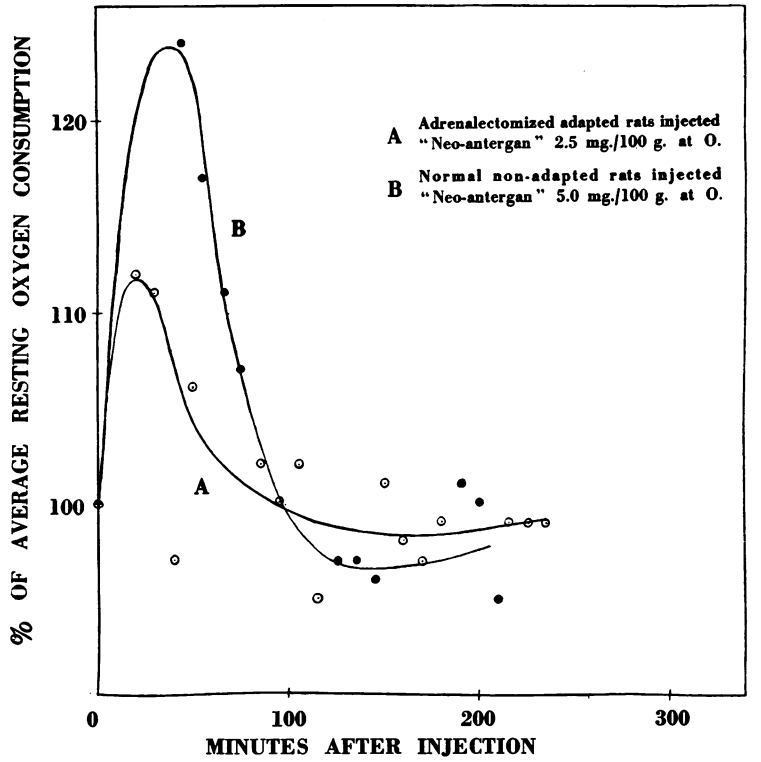

FIG. 4.—Action of neoantergan on oxygen consumption of groups of 5 rats. (1) Adrenalectomized, adapted rats, (2) normal, non-adapted rats. Increased motor activity, even convulsions and an increased O_2 consumption. Abscissae: time. Ordinates: percentage of average O_2 consumption before injection.

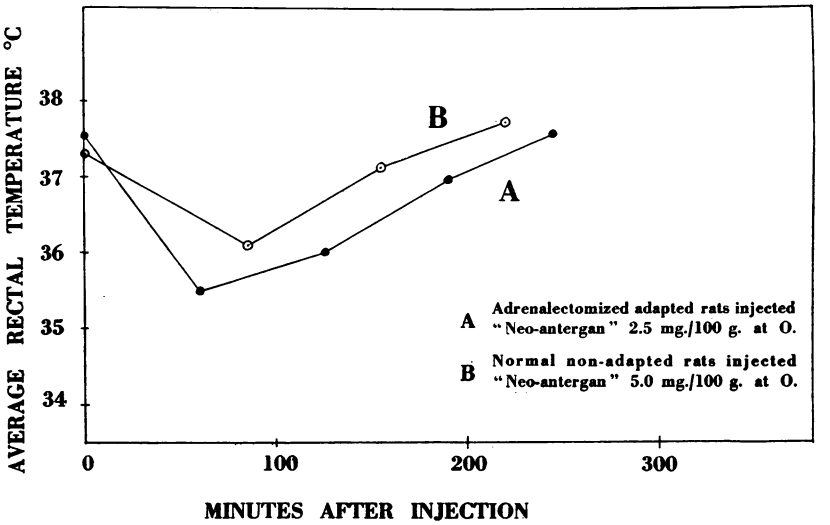

FIG. 5.—Action of neoantergan on rectal temperature of groups of 5 rats. (1) Adrenalectomized, adapted rats, (2) normal, non-adapted rats. Fall in body temperature in spite of considerable motor activity and a rise in oxygen consumption. Abscissae: time. Ordinates: average rectal temperature in °C.

In non-adapted rats injection of 5 mg. neoantergan per 100 g. was followed by an increased oxygen consumption (average, 24 per cent at 45 minutes) and an average fall in temperature of 1.2° C. at 90 minutes. Both functions were normal after three hours. In normal, adapted rats, 1 mg. neoantergan/100 g. had no effect on the rate of oxygen consumption.

In adrenalectomized, adapted rats, injection of 2.5 mg. neoantergan per 100 g. caused an average fall in temperature of 2.2° C. at one hour with only a slight lowering of the oxygen consumption after an initial increase of about 12 per cent.

3300 R.P.

This substance did not significantly alter either body temperature or oxygen consumption (Fig. 6) and had no obvious action on general activity.

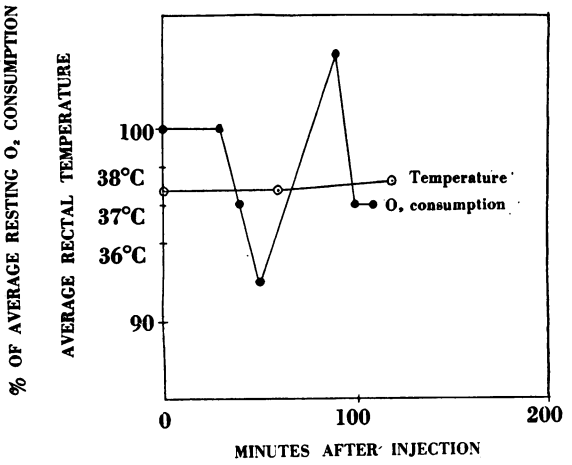

FIG. 6.—3300 R.P. (5 mg./100 g.) has no significant effect on rectal temperature or oxygen consumption in a group of 4 normal, non-adapted rats. Abscissae: time. Ordinates: average rectal temperature in °C., and percentage of average O_2 consumption before injection.

Control animals

Insignificant changes occurred in the oxygen consumption of two groups of five normal rats kept in the apparatus for some hours.

DISCUSSION

Several interesting points arise from these results. Doses of phenergan which caused only a mild and temporary increase in activity of the rat caused an initial slight rise in oxygen consumption followed by a fall both of temperature and oxygen consumption. This fall was much greater after adrenalectomy. The hypothermic action is probably at least partly due to a central effect on the temperature regulating centre. This accords well with other evidence of a central depressant action of phenergan, e.g., its well-known sedative effect when used clinically. A similar action is seen in rabbits when a small dose is injected into the third

ventricle (Halpern, 1949). In addition, phenergan has been found to be of considerable benefit in the treatment of Parkinson's disease, the site of action being central.

When large doses of phenergan are injected there is such a pronounced central motor excitation (convulsions) that the metabolic rate is increased. Even so, the temperature at first falls, perhaps because of a depressant effect on the "heat regulating centre." Later the effect of the very large increase in motor activity exceeds the central depressant action and the temperature rises slightly.

With neoantergan, both temperature and rate of oxygen consumption fell in adrenalectomized, non-adapted rats, but the effect was less than that of a large dose of phenergan.

In the normal animals, neoantergan caused considerable excitement and a greatly increased oxygen consumption, together with only a slight fall of temperature. There was certainly increased muscular activity and yet the temperature fell. This is unlikely to be due to a peripheral action and probably represents the animal's failure, in spite of convulsive muscular activity, to maintain its temperature.

Dutta's suggestion that the similar hypothermic action of procaine, etc., may be due to peripheral antagonism of acetylcholine resulting in reduced heat production from less active muscles seems inadequate to explain the effect of phenergan and neoantergan in the rat. Some interesting results were recently reported by Mahaux and Kowaleski (1949), who found that "Diparcol," which gives relief from the symptoms of Parkinson's disease, causes a fall in the rate of oxygen consumption of such patients and also in hyperthyroid subjects. The rise in metabolic rate of such hyperthyroid patients after exercise is also much less if they are given diparcol before the exercise. Diparcol is N-diethylaminoethyl-phenothiazine hydrochloride. It has actions similar to procaine in addition to being an inhibitor of pseudo cholinesterase (Gordon, 1948). Mahaux and Kowaleski consider that diparcol lowers metabolic rate by depression of the increased excitability of the higher centres controlling heat production.

The observation that equal doses of 3300 R.P. do not have the same temperature-lowering effect as phenergan suggests that the action of the latter may be related to its antihistamine activity, an activity which 3300 R.P. does not possess.

The observed increase in the sensitivity of non-adapted animals to the hypothermic and central metabolic depressant action of phenergan is particularly interesting in view of the recent work of Galvão (1947). He has shown that, in animals and men living at the relatively high and constant temperature of São Paulo, the metabolic rate is more nearly proportional to body weight than to surface area. The relation to surface area is more nearly true in relatively cooler places. Bargeton (1949) has suggested the possibility that the observed metabolic rate of men and animals in cold places is not a true "basal metabolic rate." The organism is always maintaining a temperature in excess of that of its environment. For this purpose its energy metabolism is in excess of the "true" basal metabolism. As a corollary to these observations one might expect that animals adapted to a higher temperature than that of the normal environment might show a metabolic rate more closely approximating to that which is truly basal for them and so would probably be less sensitive to the central depressant action of substances such as phenergan. Galvão

(1947) has also shown that under the conditions in São Paulo (corresponding in some degree to the conditions of the present adapted animals) there is no significant difference between the oxygen consumption of unanaesthetized dogs and that of dogs anaesthetized with dial and morphine, the rectal temperatures of the latter animals being kept at a normal level by external heating.

This increased susceptibility of non-adapted rats may throw some light on the difference between the effects on temperature observed here and those seen after equal doses of phenergan by Halpern and Briot (1949). These workers found a very considerable hypothermic effect, as much as 10° lowering of temperature, some 3–6 hours after phenergan in adrenalectomized rats. Their experiments were done during the early part of the year, in February and March, when the animals' environmental temperature was probably very much lower than that obtaining when the present experiments were done, during the heat-wave of July, 1949. This is in addition to the notorious difference between susceptibility of different animals in different laboratories.

The enhanced action of these substances in adrenalectomized animals does not appear to be secondary to an increased resting metabolism after adrenalectomy. It is, of course, well known that such animals are very sensitive to changes in environmental temperature. Methods for the assay of adrenocortical hormone take advantage of this fact, using adrenalectomized drakes and rats dying, unless treated, much more quickly at low temperatures than at high ones.

Summary

1. In rats, the fall of temperature after injection of phenergan is accompanied, often after an initial rise, by a fall in oxygen consumption. The fall in temperature often occurs at a time of increased muscular activity. It is suggested that the hypothermic effect is probably due to a central, and not to a peripheral, action.

2. Both effects are enhanced in adrenalectomized rats.

3. After neoantergan, a probable central depressant effect on the heat-regulating centre is overshadowed by the considerable convulsions of cortical origin induced by the substance.

4. A substance 3300 R.P., chemically similar to phenergan, but having no antihistamine activity and causing no fall in temperature of rats, has no significant effect on their oxygen consumption.

5. Animals which have been adapted for some months to a temperature of 29.5° C. are much less sensitive to the hypothermic and metabolic depressant action of phenergan than rats which have not been so adapted.

6. The significance of this latter result is discussed especially in relation to the recent observations of Galvão.

I must express my thanks to Dr. B. N. Halpern, at whose suggestion this work was done, for his hospitality and stimulating discussion; also to the Société Theraplix, Paris, and especially to Dr. D. Bargeton, for the hospitality of their physiological laboratory during the performance of the experimental work.

It would have been impossible to do the work without the considerable assistance of Mr. Krumm-Heller, of the same laboratory.

The work was done during the tenure of the George Herbert Hunt Travelling Scholarship, 1949.

Grateful acknowledgment is also made of an additional maintenance grant from the Medical Research Fund of the University of Sheffield.

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