Effect of Adrenaline, Noradrenaline and Chlorpromazine on Blood Pressure of Normal and Cold-Adapted Animals. (26026)

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In normal animals adrenaline, which is primarily secreted by the adrenal medulla, is essentially a metabolic activator as evidenced by its effect on oxygen consumption, adrenal ascorbic acid, etc.(1,2,3). On the other hand noradrenaline, which has little activity in that respect, is much more active on vasomotor control of blood pressure and is known as the physiological mediator of adrenergic vasomotor nerves(3,4). In animals exposed to cold for long periods of time, noradrenaline acquires a very strong calorigenic effect(5,6). However it is not known if adaptation to this stress will also change the vasomotor response to both adrenaline and noradrenaline. The present study reports the effect of these amines on blood pressure of cold-adapted rats and the effect of chlorpromazine on this response. We have shown previously that the hypothermic response to chlorpromazine is reduced in cold adapted animals(7).

Material and methods. Two groups of 10 male white rats, having a final weight of about 400 g, were used. The experimental group had been exposed to cold (10°C) for 6 months prior to test while the control group was kept for the same length of time at 25°C. The animals were anesthetized with nembutal (50 mg/kg i.p.) and heparinized. Blood pressure was measured by cannulation of the carotid and recorded on a kymograph by means of a double membrane liquid manometer. All drugs, which were given by the femoral vein, were contained in 0.2 cc volumes. Duration of all injections was 5 seconds. Both adrenaline and noradrenaline were assayed on control and experimental groups. The doses expressed in γ of the base varied between 0.07 and 10 per kg. Injections of adrenaline and noradrenaline were alternated in the same animals and time was allowed between injections for return of blood pressure to original levels. In 6 animals of each group chlorpromazine (2 mg/kg)* was injected after the initial response to adrenaline and noradrenaline had been studied. Once the constant hypotensive level following chlorpromazine injections was obtained, the response to both adrenaline and noradrenaline was again investigated.

Results. A. *Effect of adrenaline and noradrenaline on blood pressure of normal and cold-adapted rats.* The initial blood pressures of normal animals (108 $\pm$ 6) were not significantly different from those of cold-adapted animals (113 $\pm$ 5). Blood pressure increase following injections of adrenaline and noradrenaline in normal animals was directly proportional to dose and response to both substances was of the same magnitude (Table I). However, in cold-adapted rats, at doses of 0.5 and 0.2 γ/kg, response to noradrenaline was significantly greater than that to adrenaline. Similarly the response of cold-adapted rats to the 2 lower doses of noradrenaline was greater than that of normal rats. Fig. 1 illustrates these differences.

B. *Effect of chlorpromazine on blood pressure response of normal and cold-adapted rats to adrenaline and noradrenaline.* Normal and cold-adapted rats exhibited a similar hypotensive response to chlorpromazine. The quantity of chlorpromazine used (Table II) was proven completely effective in preventing the hypertensive response normally observed with adrenaline. However it was possible with a similar dose of noradrenaline to oppose to some extent the hypotensive response to chlorpromazine in both groups. Furthermore this effect of noradrenaline was significantly more pronounced in cold-adapted animals (Fig. 2).

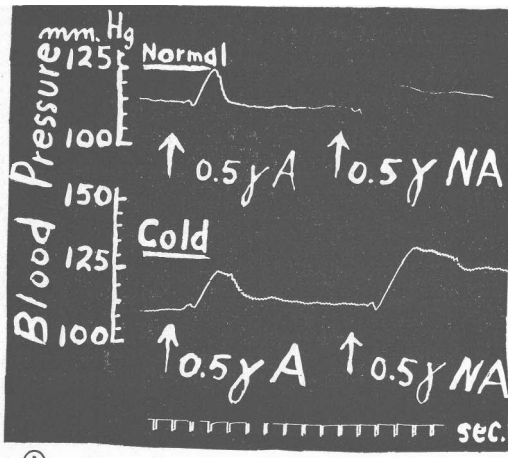
Discussion. Adaptation to cold was known to increase metabolic activity of noradrenaline (5,6). In the present study we have shown that animals adapted to this stress are also more sensitive to the cardiovascular effect of noradrenaline. Furthermore this increased

* Chlorpromazine was graciously supplied by Poulenc Ltd under their trade name Largactil.

TABLE I. Increase in Blood Pressure of Normal and Cold-Adapted Rats (10°C for 6 Months) Following Injections of Adrenaline and Noradrenaline.

Adrenaline dose (γ/kg)	Blood pressure increase (mm Hg) Normal	Cold	Noradrenaline dose (γ/kg)	Blood pressure increase (mm Hg) Normal	Cold
2	40 ± 6*	42 ± 5	2	36 ± 6	49 ± 4
1	27 ± 4	29 ± 4	1	30 ± 9	38 ± 2
.50	13 ± 3	14 ± 3	.50	14 ± 3	†*26* ± *3*
.25	5 ± 2	8 ± 3	.25	7 ± 3	†*25* ± *2*

* Stand. error. † Significant at 1% level.



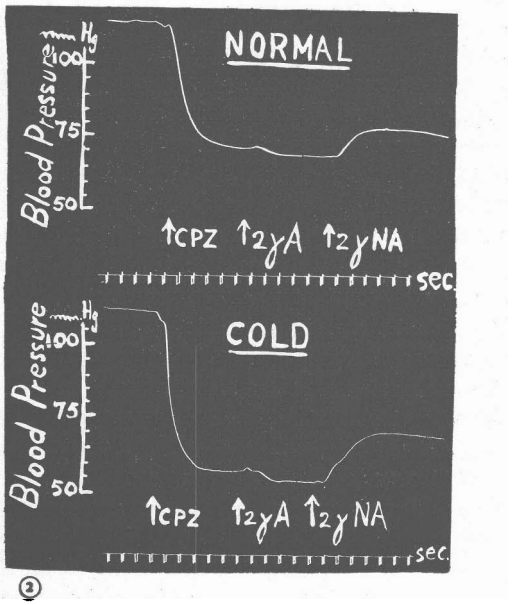


FIG. 1. Blood pressure response of normal and cold-adapted (10°C for 6 mo) rats to adrenaline and noradrenaline i.v. injections.

FIG. 2. Effect of CP2 (chlorpromazine at 2 mg/kg) followed by adrenaline and noradrenaline in normal and cold-adapted (10°C for 6 mo) rats.

reactivity of cold-adapted animals to noradrenaline is observed only when smaller doses are given, *i.e.*, doses approaching physiological levels.

As pointed out by Von Euler(3) most of the adrenolytic agents and many antihistamines(8) antagonize much more the circulatory effects of adrenaline than of noradrenaline. This is also true, as we have shown, for chlorpromazine which is known to possess adrenolytic and antihistaminic action. Furthermore after adaptation to cold noradrenaline is more active than normally in opposing the hypotensive effect of chlorpromazine. Thus here also animals adapted to cold are more sensitive to noradrenaline than non-adapted animals.

This increased responsiveness of cold-adapted animals to noradrenaline may be related to recent results indicating that these adapted animals excreted much more noradrenaline than normal animals(9).

Summary. The blood pressure response of normal and cold-adapted rats to adrenaline, noradrenaline and chlorpromazine was studied. Adaptation to cold increased the re-

TABLE II. Change in Blood Pressure in Normal and Cold-Adapted Rats (10°C for 6 Months) Injected with Chlorpromazine Followed by Adrenaline and Noradrenaline.

Substance inj.	Blood pressure changes (mm Hg) Normal	Cold
Chlorpromazine (5 mg/kg)	−41 ± 8*	−53 ±11
Chlorpromazine + adrenaline‡ (2 γ/kg)	− 3 ± 1	− 1 ± 1
Chlorpromazine + noradrenaline‡ (2 γ/kg)	7 ± 2	† *18* ± *3*

* Stand. error.
† Significant at 1% level.
‡ Difference between (chlorpromazine) and (chlorpromazine + adrenaline) or noradrenaline.

sponsiveness to noradrenaline but not to adrenaline. The hypotensive response to chlorpromazine was the same in normal and cold-adapted rats and adrenaline did not oppose this effect in both groups. However noradrenaline, which normally slightly antagonized the hypotension of chlorpromazine, was much more effective in that respect when tested on cold-adapted animals. Cold adapted animals were known to be more sensitive to the metabolic effect of noradrenaline; the present study indicates that this increased responsiveness to noradrenaline also exists for its cardiovascular effect.

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Gonadotropic Antiserum Effects in Normal and Irradiated Female Mice.* (26027)

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Antisera to crude sheep pituitary extract with antigonadotropic properties inhibited development and differentiation of ovaries transplanted to the spleen of castrate mice and modified changes usually seen in mouse ovaries after irradiation(1,2). The effects of sera with pituitary antigonadotropic properties upon reproductive organs of normal animals have been differently recorded by others and experimental circumstances have varied (3-7). Therefore, it was deemed necessary to extend observations made on experimentally altered animals to normal young adults using the same materials and procedures. Particular attention was given to gonadotropic content of pituitary glands.

Materials and methods. Female mice of the MFl strain‡ 60-70 days of age at time of first injection were used. Two-tenths ml of antigonadotropic serum was injected subcutaneously daily 5 times a week for 6 weeks. Controls received normal rabbit serum, sheep heart antiserum, or saline; others were not injected. Some mice were x-rayed with injection starting the day after total body exposure to 175 r.§ Details of the method of preparation and assay of antiserum have been given (1,2.8). Briefly, the antiserum is developed by injection of sheep pituitary extract into rabbits until a gonadotropic antagonistic effect appears in the serum. The effect is demonstrable when pituitary extract (the antigen) and antigonadotropic serum (the antibody) are injected simultaneously, but separately, into immature female mice. Preparations comparable to those used in this study inhibit endogenous gonadotropins(9) and are aspecific(10). Thyrotropic activity is measurable,‖ but there appear to be negligible amounts of lactogenic activity. And, on the basis of short term assays, there is little adrenocorticotropic or growth hormone ac-

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‡ Purchased from Manor Farms, Staatsburg, N. Y.

§ Physical factors have been given in detail in (2).

‖ Preliminary studies do not indicate that I^{131} uptake after injection of pituitary extract is altered.