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RESPONSES OF COLD- AND WARM-ADAPTED DOGS TO INFUSED NORADRENALIN AND ACUTE BODY COOLING

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ARCTIC AEROMEDICAL LABORATORY

AEROSPACE MEDICAL DIVISION
AIR FORCE SYSTEMS COMMAND
FORT WAINWRIGHT, ALASKA

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FOREWORD

This is one of five parts of the final report to be prepared under contract AF 41(609)-2193 (Project 8237, Task 823702) with the Department of Physiology and Biophysics, University of Kentucky, Lexington, Kentucky. This report covers research carried on from October 1963 to November 1964. Air Force program monitor is Dr. Eugene Evonuk, ALRP, Arctic Aeromedical Laboratory.

This technical report has been reviewed and is approved.

PUBLICATION REVIEW

HORACE F. DRURY
Director of Research

ABSTRACT

A total of 12 experiments was done in cold-adapted (C-A) and warm-adapted (W-A) beagle dogs, kept more than 40 days at -10° C and 28° C, respectively. The animals, anesthetized with pentobarbital sodium (30 mg/kg), were paralyzed with Flaxedil (5 mg/kg/hour) and mechanically ventilated at 28-30° C. Oxygen consumption, heart rate and colonic, pinna and paw skin temperatures were measured continuously. The dogs were infused with noradrenalin (1.25 μg/kg/min) for 20 minutes at 30° C and after 45 minutes of acute cold exposure to 5° C. At 28-30° C, basal 0_2 consumption was higher in C-A dogs. Oxygen consumption of C-A dogs increased with a slight increase in the heart rate during the initial 18-20 minutes after body cooling and then decreased. In W-A dogs, 0_2 consumption decreased continuously after acute cold exposure. Calorigenic effects of infused noradrenalin were consistent in C-A and W-A dogs at 30° and 5° C, but there was no difference between the increased amount of 0_2 consumption from the initial levels in both groups. Noradrenalin caused an increase of the heart rate in W-A dogs at 30° and 5° C, with decrease or no change in C-A dogs. Colonic, pinna and paw skin temperatures were significantly higher in C-A than in W-A dogs. Noradrenalin caused an increase in the temperatures, but the effect of the drug was more prominent in W-A than in C-A animals at lower temperature. These results suggest that the mechanism of nonshivering heat production is well developed by cold acclimation in dogs, and that the increase of this mechanism is due rather to the increase of noradrenalin content in blood than to increased sensitivity of the animals to the calorigenic effects of noradrenalin.

I

INTRODUCTION

Hsieh and Carlson (1, 2) showed that nonshivering thermogenesis and calorigenic effects of noradrenalin are enhanced in cold-acclimatized rats. This was confirmed by a series of papers (3, 4, 5, 6, 7, 8), but relatively few have reported on this in other animals. There are observations of a decrease in shivering after prolonged cold exposure in other mammals, including man (9, 10, 11). The indication is that the mechanisms involved in cold acclimation in other mammals are the same as those in rats. Infusion of noradrenalin produced a significant increase in oxygen consumption in cold-acclimated men (12, 10). This suggests that an increased sensitivity to noradrenalin is the probable mechanism of an increase of nonshivering heat production after prolonged cold exposure.

In this paper, observations on nonshivering thermogenesis are extended by study of the effects of noradrenalin infusion in cold- and warm-adapted dogs at various temperatures. The effect of this hormone on nonshivering thermogenesis in dogs will be discussed.

II

METHODS

Four male beagle dogs, with an average weight of 9.95 kg, were used repeatedly in these experiments. Cold acclimatization was induced in two of the animals by putting them in a cold room (-10° C) for more than 40 days. The other two dogs were maintained in a warm room (28° C) for an equal length of time. Of a total of 12 experiments, the first group of experiments were done after five weeks of cold acclimatization, and the second and third groups were done four and seven weeks, respectively, after the first group.

In the first and the second experiments, the animals were brought into the laboratory (28-30° C) and anesthetized with pentobarbital sodium (30 mg/kg). Following anesthesia, a polyethylene catheter was inserted into the saphenous vein of a hind leg for noradrenalin infusion. After the surgical procedure, the animals were moved into a cooling box and mechanically ventilated. One hour after anesthesia, the animals were paralyzed with Flaxedil (5 mg/kg/hour) and resuscitated for 30 minutes at 28°C. Then the

animals were cooled by cold air (5° C at 800-1000 ft/min). After 45 minutes of cooling, infusion of noradrenalin (1.25 μg/kg/min) was initiated and continued for the following 20 minutes. In the third experiment, the animals were kept at 28-30° C, and after a 20-minute resuscitating period under Flaxedil (5 mg/kg/hour), 1.25 μg/kg/min of noradrenalin was infused during the following 20 minutes.

During the experiments, expired gases were analyzed continuously by a Beckman oxygen analyzer (Model E2), and O_2 consumption (S.T.P.D.) was calculated. The volume of the expired gases was determined by a wet type gas meter (Precision). Colonic, pinna and paw skin temperatures were continuously recorded from copper-constantan thermocouples on a Brown electronic potentiometer. Thermocouples were fastened on the inner surface of the ear and also on the paw with Eastman 910. Electrocardiograms and muscle activity from the electrodes in the triceps muscles were recorded continuously on a Gilson minipolygraph.

III

RESULTS

The dogs exposed to cold lost approximately 8% of their body weight during 40 days of cold exposure, while the animals in the warm room lost only 4% of their weight. Food consumption of the dogs exposed to cold was approximately 54 gm/kg/day, which was 30% higher than both the initial food consumption of this group measured prior to cold exposure and that of the warm-adapted animals.

The initial O_2 consumption (measured at 30° C) was slightly higher in cold-adapted (C-A) dogs (6.60 ml/kg/min). The infusion of noradrenalin (1.25 μg/kg/min) caused a marked increase of O_2 consumption in both warm adapted (W-A) and C-A dogs, and the maximal O_2 consumption during the infusion of noradrenalin was higher in C-A animals (10.33 ml/kg/min) than in W-A animals (9.75 ml/kg/min). Immediately after the stopping of the infusion, O_2 consumption decreased sharply to new levels which were higher (8.35 ml/kg/min) than the initial levels (Figure 1).

Effects of Flaxedil (5 ml/kg/hour) and of noradrenalin on the heart rate were different in both groups. Before curarization, the heart rate was 150 beats/min in both groups. The infusion of Flaxedil caused an increase in the heart rate in the W-A group (168 beats/min) without any significant change in the C-A group. The heart rate increased up to 210 beats/min within 2-3 minutes of the infusion of noradrenalin in the W-A dogs and was maintained 182 beats/min throughout the next infusion. After the infusion

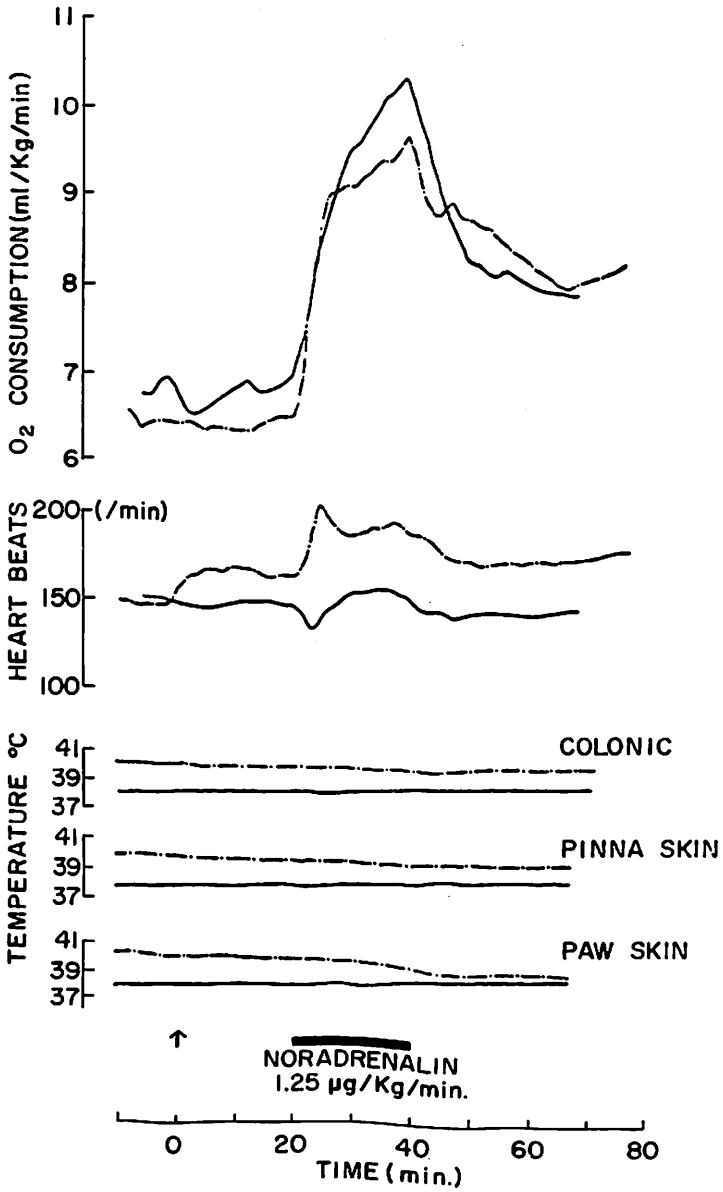

FIGURE 1

Effects of Noradrenalin Infusion on O_2 Consumption, Heart Rate and Colonic, Pinna and Paw Skin Temperatures at Ambient Temperature of 30° C.

Solid bar indicates infusion of noradrenalin (1.25 µg/kg/min), and arrow shows starting point of Flaxedil infusion (5 mg/kg/hr). Solid lines indicate results from cold-adapted dogs, and broken lines, warm-adapted dogs.

was stopped, the heart rate returned to a new level slightly higher (174 beats/min) than that before the infusion of noradrenalin. The heart rate of the C-A dogs fell to approximately 130 beats/min after 2-3 minutes of the noradrenalin infusion, and then it returned to slightly above the initial level. In cold-adapted dogs, the effect of noradrenalin was limited to the duration of the infusion of the drug (Figure 1).

The colonic, pinna and paw skin temperatures were higher in W-A animals than C-A ones at the ambient temperature of 30° C. The difference between the temperatures in W-A and C-A was 2° C at the beginning of the experiment. The infusion of 1.25 μg/kg/min of noradrenalin caused a very slight increase of the colonic temperature (0.1° C) in the W-A group, with no change of the pinna skin temperature and with a slight decrease of the paw skin temperature. The colonic, pinna and paw skin temperatures in C-A dogs increased approximately 0.5°, 0.5° and 0.7° C, respectively, after the infusion of noradrenalin.

Oxygen consumption and heart rate of C-A dogs increased during the initial 18-20 minutes after cooling, and then decreased (Figure 2). On the other hand, O_2 consumption of W-A dogs continued to decrease after cooling, so that the difference between the O_2 consumption of the two groups was greater during the body cooling than in the normal condition (Table I).

The infusion of noradrenalin caused an increase in O_2 consumption in both groups, but the increase was less during body cooling than in a warm environment. An abrupt increase in O_2 consumption was more prominent in W-A than in C-A animals. The heart rate increased in W-A dogs, without any significant change in C-A dogs, by the infusion of noradrenalin.

After 40 minutes of body cooling, there was no difference between the colonic temperatures in W-A and in C-A animals. However, the infusion of noradrenalin raised the colonic temperature slightly in the C-A group without any significant change in the W-A animals. The pinna skin temperature during body cooling was significantly higher in C-A animals than in W-A ones. In the paw, skin temperature in W-A animals decreased greatly while the decrease in C-A animals was less marked. However, the effect of noradrenalin infusion on the skin temperature was more prominent in W-A than in C-A animals. After stopping the infusion, skin temperatures fell to a lower level than they were before the infusion (Figure 2).

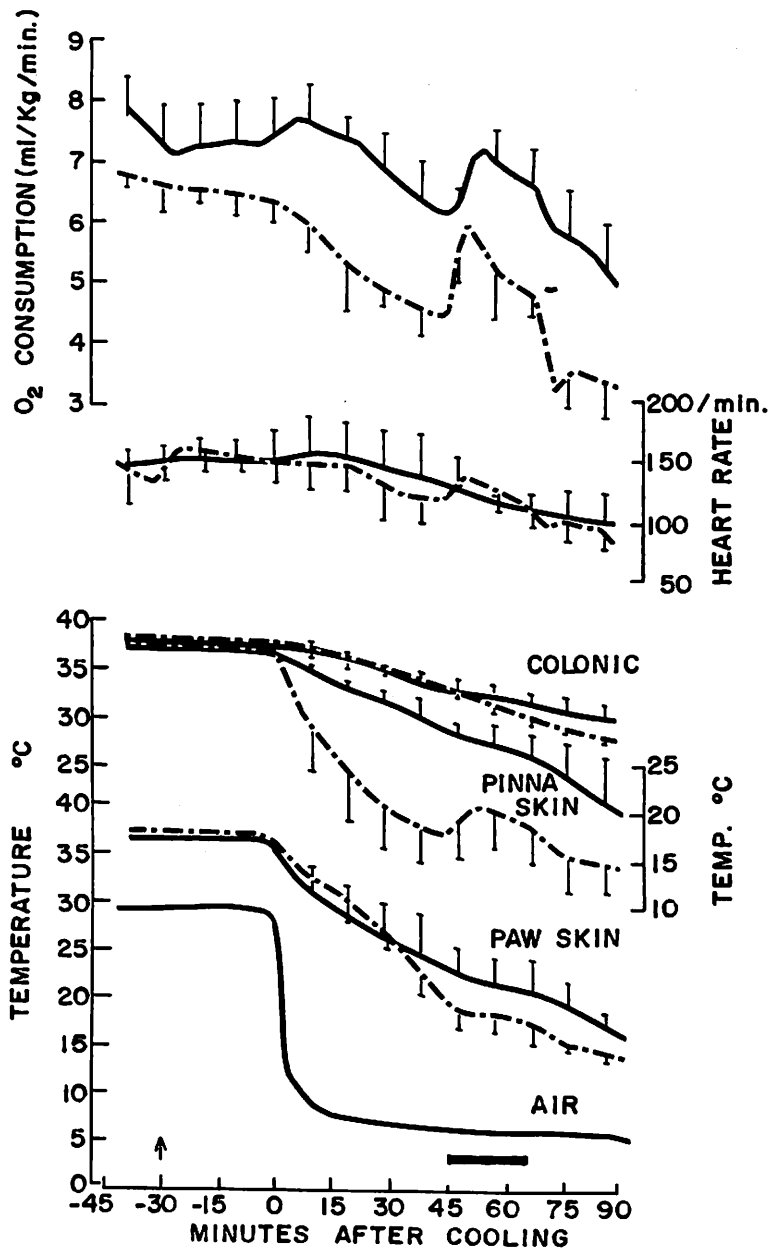

FIGURE 2

Changes in O_2 Consumption, Heart Rate and Temperature of Curarized Dogs with Lowered Ambient Temperature.

Solid bar indicates infusion of noradrenalin (1.25 ug/kg/min), and arrow shows starting point of Flaxedil infusion (5 mg/kg/hr). Vertical lines indicate standard deviations. Solid lines show results from cold-adapted dogs, and broken lines, warm-adapted dogs.

TABLE I

Minutes after Cooling	C-A Heart Rate	W-A Heart Rate	C-A O_2 Consumption	W-A O_2 Consumption	(C-A – W-A) Difference in O_2 Consumption
-38	148 ± 12	144 ± 27	7.77 ± .62	6.81 ± .25	.96
-28.5	153 ± 12	153 ± 13	7.18 ± .81	6.56 ± .39	.62
-19	156 ± 16	164 ± 19	7.28 ± .46	6.61 ± .30	.67
-9.5	157 ± 19	161 ± 16	7.39 ± .74	6.42 ± .31	.97
0	154 ± 19	154 ± 17	7.44 ± .62	6.40 ± .33	1.04
9.5	161 ± 27	153 ± 23	7.67 ± .61	5.89 ± .47	1.78
19	156 ± 31	152 ± 23	7.40 ± .30	5.31 ± .81	2.09
28.5	144 ± 35	134 ± 30	6.78 ± .72	4.90 ± .33	1.88
38	140 ± 39	124 ± 25	6.34 ± .70	4.53 ± .40	1.81
**					
47.5	129 ± 28	140 ± 8	6.10 ± .43	5.62 ± .71	.48
57	118 ± 4	129 ± 18	6.87 ± .66	5.16 ± .82	1.71
66.5	111 ± 11	111 ± 10	6.58 ± .58	4.82 ± .40	1.76
76	105 ± 16	101 ± 22	5.60 ± .77	3.57 ± .60	2.03
85.5	100 ± 25	91 ± 14	4.93 ± .07	3.35 ± .53	1.58

**Between the two lines — infusion of noradrenalin

IV

DISCUSSION

Calorigenic effects of noradrenalin were consistent in both C-A and W-A dogs at normal and cold ambient temperatures. Twenty-minute infusion of 1.25 μg/kg/min of noradrenalin caused an immediate increase of O_2 consumption in both groups, but this response was limited to the infusion period. After the infusion, O_2 consumption decreased to new levels, which were relatively higher than those before the infusion. This may be due to residual calorigenic effects of the small amount of noradrenalin taken up in the various tissues.

During the infusion, no significant difference was observed in the increased amount of O_2 consumption from the initial levels in both groups, but the total O_2 consumption during this period was significantly higher in C-A dogs than in W-A ones. The capacities to increase heat production by exogenous noradrenalin in C-A and W-A animals seem to be the same. The infusion of noradrenalin caused the colonic temperature to increase, especially in the cold-adapted group. On the other hand, 1.25 μg/kg/min of noradrenalin caused a consistent increase of skin temperature in W-A dogs at a lower room temperature. The decrease of skin temperature observed in rats (13) and in rabbits (14) was not observed in dogs with the concentration of noradrenalin used.

Noradrenalin (1.25 μg/kg/min) caused an increase of the heart rate in the W-A group during the infusion, with a slight decrease or no change in C-A dogs at lower ambient temperatures. Thus, the increase in the skin temperature of W-A dogs, without an increase in the colonic temperature, would be due to improvement of cardiovascular performance by infused noradrenalin. The threshold of cardiovascular responses to noradrenalin is increased by cold acclimation. Since the noradrenalin level in blood is elevated by cold acclimation (7, 8), this increase of threshold may be a reasonable explanation of the lesser change in skin temperatures of C-A dogs by exogenous noradrenalin.

In dogs, the infusion of noradrenalin results in a response different from that reported in rats (1, 2, 15, 16) and rabbits (14). There is a decrease in heart rate in the C-A animals and no difference in augmenting effects of noradrenalin to the O_2 consumption in W-A and C-A animals. This discrepancy between the earlier concepts in rats and in men and those observed in this experiment may be attributed either to the difference in the amount of noradrenalin infused or to the great difference in sensitivity to noradrenalin in various animals.

Basal O_2 consumption in C-A dogs was higher than in W-A dogs at 28-30° C. The increase of O_2 consumption after body cooling in C-A animals, without an increase in W-A ones, explains that the mechanism of nonshivering heat production is well developed by cold acclimation. A higher basal O_2 consumption in C-A animals and no significant difference in the calorigenic effects of the infused noradrenalin in both groups may suggest that the increase of nonshivering heat production during cold acclimation is due rather to the increase of noradrenalin content in blood than to the increased sensitivity of the animals to the calorigenic effects of noradrenalin.

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