Effect of Chronic Exposure to Hypoxia on Development and Maintenance of Renal Hypertension in Rats[1] (34732)

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Natives of the Andes who live and work at high altitudes have both a lower blood pressure and a reduced incidence of hypertensive cardiovascular disease when compared with individuals of similar age living at sea level (1). It has also been reported that natives of Ceylon living at an altitude of 6000 feet have systolic blood pressures which average about 10 mg Hg less than those living at sea level (2). Reasons for the lower blood pressure and reduced incidence of hypertensive disease are unknown but could be related to either physiologic, genetic, or environmental factors or combinations of these. Studies using rats have been performed in this laboratory to determine the effect of exposure to hypoxia on the development of experimentally induced renal hypertension (3). The results indicated that chronic exposure to an atmosphere containing 13% oxygen protected rats against the development of hypertension in that systolic blood pressure failed to rise to the level observed in controls. In this study, mean food intake of the treated group was depressed during the first 3 weeks of exposure to hypoxia. Since anorexia is known to reduce blood pressure (4), the experiment described below was carried out to estimate the contribution of anorexia to the blood pressure depressing effect of hypoxia. In addition, the effect on blood pressure of removal from hypoxia was studied to determine whether the protection against hypertension afforded by hypoxia was permanent or temporary.

Methods. Twelve male rats of the Holtzman albino strain weighing from 240 to 260 g were used. During a 2-week control period, systolic blood pressure was measured three times on each unanesthetized rat by the microphonic manometer technique of Friedman and Freed (5) as modified for use in this laboratory (6). Body weight was also measured once weekly. The rats were kept 3 to a cage in thermoregulated room maintained at 26° and illuminated from 8 a.m. to 6 p.m. during both control and experimental periods. All rats were given tap water to drink and ground Purina laboratory chow to eat. Water was available at all times in containers of the type described by Lazarow (7). These consisted of infant nursing bottles with cast aluminum spouts. Food containers were essentially spill-proof and have been described in detail (8).

At the end of the 2-week control period, the kidneys of all rats were bilaterally encapsulated with latex envelopes by the method of Abrams and Sobin (9). Three days were allowed for recovery from the operation after which half of the rats (6 in all) were placed in a chamber and subjected to hypoxia by the gas dilution technique of Sisson and Fregly (10). The remaining 6 rats were not subjected to hypoxia and served as controls for the treated group. During the first day of exposure to hypoxia, the percentage of oxygen in the chamber was reduced to 17%. Thereafter the percentage of oxygen in the chamber was reduced by 1%/day until the rats were living in an atmosphere containing 13% oxygen. The fraction of oxygen in the chamber remained at this level until the end of the experiment, 15 weeks later. The average barometric pressure during the experimental period was 754.8 mm Hg.

The chamber was opened every second day to weigh the rats, measure food and water intakes, replenish the carbon dioxide (soda lime) and water vapor (concentrated sulfuric

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acid) absorbers and to clean the cages. The time required to make these measurements was approximately 1 hr. Hence, the rats subjected to hypoxia were returned to 21% oxygen for 1 hr out of every 48. Once each week, during the time the chamber was opened, systolic blood pressure of each rat was measured. This measurement necessitated keeping the rats in 21% oxygen for an additional 1.5 hr.

Paired-feeding began at the time of the initial exposure to hypoxia. This consisted of allowing sea level controls only the amount of food to eat that hypoxia-treated rats consumed during the previous 2-day period. In this way an attempt was made to match the food intakes of the two groups. Paired-feeding ended at the end of the 14th week of exposure to hypoxia. Water intake of each cage of 3 rats was also measured every 2 days at the time the chambers were opened.

After removal from hypoxia at the end of the 15th week, blood pressures were measured twice weekly for an additional 6 weeks.

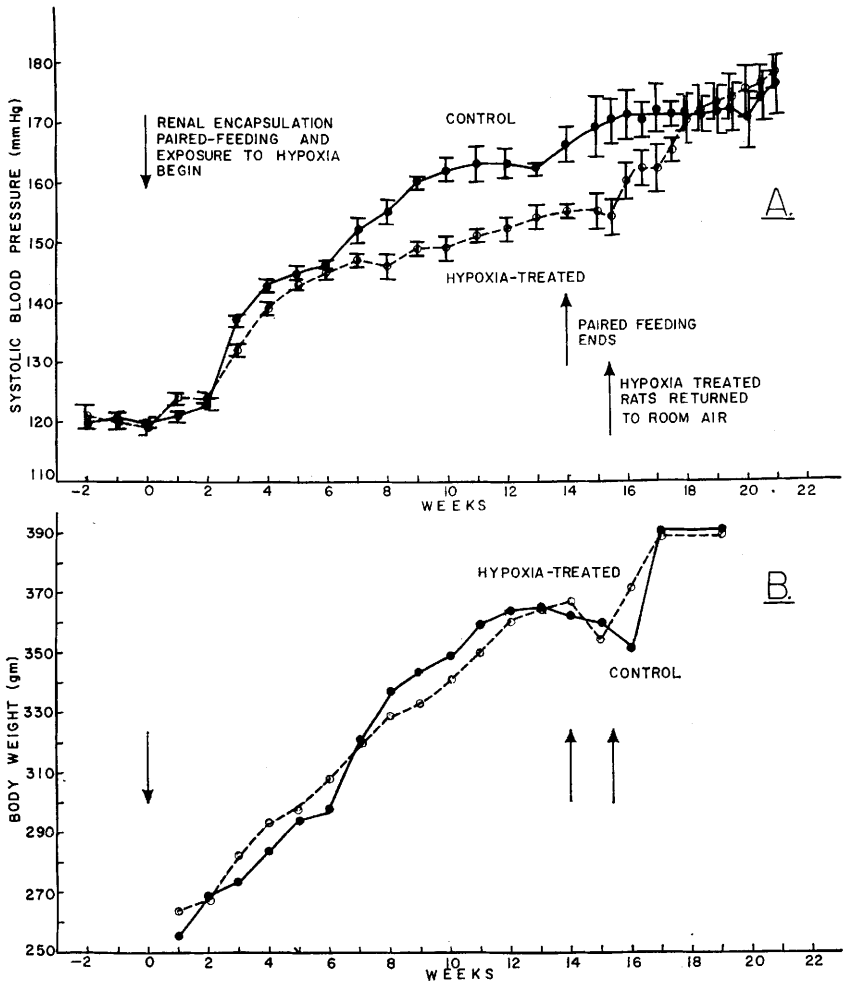

FIG. 1. The effect of exposure to an atmosphere containing 13% oxygen on development of renal hypertension in rats. Renal encapsulation with latex envelopes, paired-feeding and exposure to hypoxia began at the time designated as 0 on the graph. Paired-feeding ended during the 14th week of exposure to hypoxia and all treated rats were removed from hypoxia at the end of the 15th week. Blood pressures (A); and body weights (B) of control and treated rats are shown throughout the experiment. One standard error is set off at each mean.

Statistical analyses were performed by means of the t test for the 95% confidence limit (11).

Results. Exposure of rats to an atmosphere containing 13% oxygen prevented the rise of systolic blood pressure to the level of renal-encapsulated controls maintained in 21% oxygen (Fig. 1A). The first significant difference ($p<0.01$) between the blood pressures of the two groups occurred during the 8th week of exposure to 13% oxygen and was maintained throughout the period of exposure to hypoxia. Although protection was not complete in that blood pressures rose significantly above the levels measured prior to renal encapsulation, blood pressure level of the treated group was maintained below that of controls.

When the treated group was returned to room air (21% oxygen), systolic blood pressure gradually increased and was identical with that of controls within 2.5 weeks (Fig. 1A). The difference between mean blood pressures of the two groups was no longer significant by 1 week after exposure to hypoxia ended.

Body weights of the two groups of rats were similar throughout the experiment (Fig. 1B). During the 14th week, one control rat refused to eat, lost weight and subsequently died during the 16th week. One experimental animal also died during the 15th week. The cause of death was not determined in either case. The decrease in the body weight curves of both groups during the 14th through 16th weeks reflect these deaths.

Mean water intakes of the two groups were similar throughout the experiment (Fig. 2A) as were also mean food intakes (Fig. 2B). The latter was to be expected since the animals were pair-fed.

Discussion. Rats rendered hypertensive by latex encapsulation of their kidneys and subjected to an atmosphere containing 13% oxygen gained significant protection against development of hypertension. These results are in accord with those of a previous study from this laboratory (3) and suggest that either one or a number of the physiological changes occurring in response to hypoxia contributes to the protection observed. The possibility that the anorexia characteristically accompanying exposure to hypoxia was responsible for the protection observed was ruled out by the paired-feeding technique used in this experiment. Food intakes of the two

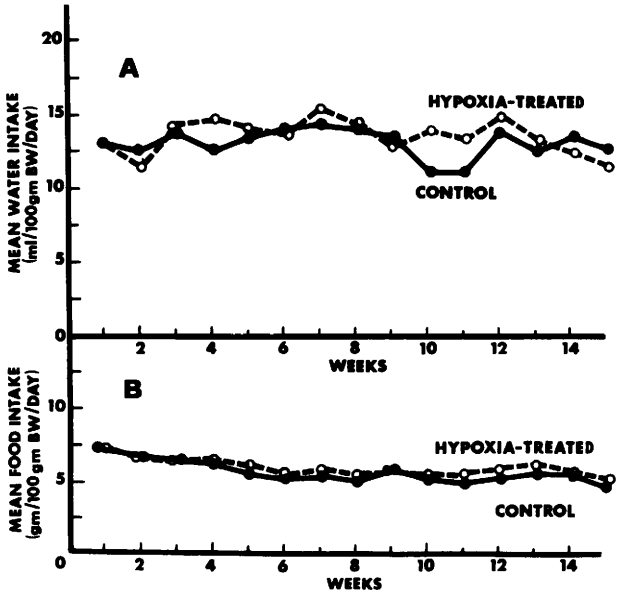

FIG. 2. Mean water (A); and food (B) intakes of control and treated rats are shown for the period of exposure to hypoxia.

groups of rats were closely matched throughout the period of exposure to hypoxia (Fig. 2B).

Results of earlier studies suggest that the thyroid gland contributes, at least secondarily, to the development of renal hypertension in rats (12). Since chronic exposure to hypoxia is reported to depress the activity of the thyroid gland (13–15), the possibility exists that the protection against hypertension afforded by hypoxia may be due either in whole or in part to a depression of thyroid activity. It cannot be stated at present to what extent reduced thyroid activity contributes.

Other physiological changes occurring in response to hypoxia may contribute to the protection against hypertension, *e.g.*, reduced vascular reactivity to normal or increased titers of circulating pressor agents and changes in acid–base balance. Although neither of these was studied in the present experiment, it is possible that renal compensation of the respiratory alkalosis of the treated rats prevented the gradual accumulation of sodium and expansion of extracellular volume which may accompany development of hypertension (16). The possibility also exists that renal compensation of the respiratory alkalosis is brought about by a reduced secretion of aldosterone, the adrenocortical hormone which regulates renal loss of sodium and potassium. Decreased secretion of aldosterone could contribute to the protection afforded by hypoxia against the development of hypertension since hypersecretion of aldosterone is often implicated as an etiologic factor in development of hypertension (17).

The results of this study indicate that the protection against hypertension afforded by hypoxia is not permanent. Upon return to normal ambient oxygen tension, blood pressure increased to the level of untreated controls, thus, the factors responsible for the protection against hypertension when rats are exposed to hypoxia are associated with the physiological changes induced by the altered environment. The possibility that certain of these changes may be induced without hypoxia provides avenues for future research. It is important to note, however, that intermittent exposure to hypoxia has been reported to elevate the blood pressure of rats (18). The difference between the physiological changes induced by intermittent and chronic exposures to hypoxia may provide important clues.

Summary. Exposure of rats to an atmosphere containing 13% oxygen immediately after encapsulation of their kidneys with latex envelopes prevented the elevation of systolic blood pressure to the level of encapsulated controls maintained in an atmosphere containing 21% oxygen. The protection afforded remained only as long as the rats were exposed to hypoxia. Following return to 21% oxygen, mean blood pressure of the treated group was identical with that of untreated controls within 2.5 weeks. Paired-feeding of the control animals to match their food intake with that of the rats exposed to 13% oxygen assured that the protective effect of hypoxia was not related to an accompanying anorexia. The mechanism responsible for the protection observed is unknown but may be associated with one or a number of the physiological and biochemical changes induced by hypoxia.

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