Alterations in Organ Weights of Mice after High Altitude Exposure*

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Abstract Male and female mice of the ICR-JCL strain born at sea level were weaned at the third week after birth and divided into five groups at random. Each group was taken to five experimental stations, at sea level and 770 m, 1,400 m, 2,000 m and 2,600 m above sea level respectively, where they were fed for seven weeks until the tenth week after birth. They were returned to sea level at this time, and were necropsied at the eleventh, fifteenth and twenty-second weeks after birth. Weights of the brain, heart, liver, kidney, spleen, adrenal gland and gonad were measured. Influences of high altitude exposure were studied by analysis of variance concerning these measurements in organ weight per body weight (%).

Results obtained were as follows: Weights of heart (in males and females), adrenal gland (in females) and kidney (in males) increased in groups exposed at 2,000 m and 2,600 m above sea level, at the eleventh week after birth. Increasing patterns of heart weight influenced by altitude, differed in each litter, depending on their sensitivities. The mice reared at high altitude environment during their raising term, their gains of body weights after returning to the sea level station were greater than that of those which remained at sea level. Especially in female mice at the twenty-second week after birth, the difference between both groups was significant remarkably. Adrenal gland weight increase, influenced by altitude exposure, appeared to be reversible and disappeared in a short period after returning to sea level.

At the present time, the feeding area of domestic animals in Japan is shifting towards the mountainous regions. For practical application of these environments in the animal management, fundamental studies, on the influences of altitudes and the adaptability of animals, must be performed.

Studies on the mechanism of adaptability to high altitude environments were published as early as 1875, and many systematic surveys of high altitude natives and experimental studies on adaptability of men and animals have appeared since 1950^{1,2)}.

Many of these works concerned altitudes from 3,000 m to 6,000 m above sea level or on the mechanism of high mountain diseases^{3,4,5)}. Especially in cattle, these studies were limited to the Brisket Disease⁶⁻¹²⁾. These works reported the dysfunction of the cardiorespiratory system, such as pulmonary hypertension or right ventricular hypertrophy, and/or renal or liver functions, as a result of low pressure and low oxygen tension in the high altitudes.

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Cardiac hypertrophy is an important change effected by high altitude exposure, but this change is not observed in environments under 3,000 m above sea level.

In Japan, the altitudes being developed for animal feeding are expected to be restricted to areas from 500 m to 2,000 m above sea level. In the cattle reared at altitudes from 1,400 m to 1,600 m, cardiac hypertrophy was observed in electrocardiograms of sixty percent of the animals but no circulatory disturbances were observed^{13,14}.

Materials and Methods

The present experiment was carried out for two years from 1968 to 1969. Male and female mice (ICR-JCL strain), born at sea level (Tokyo), were weaned at the third week after birth, and divided into several groups at random. These mice were carried to the experimental stations by the car (about six hours travelling time), and thereafter were exposed for seven weeks. Courses by car was selected so as to avoid passing higher altitudes than the area of exposure. At the tenth week after birth, the animals were returned to sea level station by the same routes. At the eleventh, fifteenth and twenty-second weeks after birth, the animals were necropsied and organ weights of the brain, heart, liver, spleen, kidney, adrenal gland and gonad were measured.

In 1968, one hundred and fifty-six mice (75 males and 81 females) were produced in fifteen litters at sea level, and distributed to the stations at altitudes of 770 m (Ina), 1,400 m (Kiyosato), 2,000 m (Utsukushigahara) and 2,600 m (Komagatake). These animals were necropsied at the eleventh week after birth. In 1969, three hundred and twenty-one mice (157 males and 164 females) were produced in twenty-six litters at sea level, and from these mice, one hundred and eighty (90 males and 90 females) were selected and divided into nine groups at random. Three groups each were distributed to the stations at altitudes of 770 m and 1,400 m. After returning to the sea level station at the tenth week after birth, each group was necropsied at the eleventh, fifteenth and twenty-second weeks after birth respectively.

Differences among the altitude exposed were examined closely by analysis of variance ($\alpha=0.05$) of the measurements. Five mice were reared in each aluminium cage covered with wood shreds, and were given water and food pellets.

Results and Discussion

The four experimental stations are located in the mountainous areas of the Central Alps in Japan, and their meteorological environments are characteristic of higher altitudes in Japan.

A correlation chart between body weight and heart weight of the wild mice (*Apodemus specicus* and *Microtus montebelli*), trapped in an experimental station at 1,400 m above sea level, and of the ICR-JCL strain laboratory mouse is shown in Fig. 1. Heart weights of the wild mice are relatively greater than those of the laboratory mice born at sea level. In *Rattus norvegicus* and *Apodemus argenteus* captured at various altitudes, heart weights became greater in proportion to the altitude^{15,16}. It is presumed that the right ventricular hypertrophy in these cases is a morphological change due to adaptation to the low oxygen tension environment of high altitudes. Using the mouse, cardiac hypertrophy effected by the high altitude exposure is expected to be observed.

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Table 1. Mean values (upper) and standard deviations (lower) in body weight (g) and organ weight per body weight (%/100): BW (3W) and BW (11W) indicate the values at the third week (before exposure) and at the eleventh week (after exposure) after birth respectively.

Sex	Male					Female				
Altitude (m)										
Organ	sea level	770	1400	2000	2600	sea level	770	1400	2000	2600
BW (3W)	9.1 1.3	9.5 1.8	9.9 0.8	9.3 1.4	9.4 2.0	9.0 1.9	9.6 1.8	9.0 2.0	9.4 2.1	9.4 1.9
BW (11W)	38.0 2.9	38.0 3.5	37.4 3.7	36.6 2.8	36.2 3.2	28.8 3.8	30.4 5.1	31.1 4.1	28.9 3.2	29.0 2.2
Kidney	15.7 2.2	17.0 1.9	17.4 1.7	18.4 2.0	19.1 2.1	12.7 1.4	13.6 1.7	13.5 1.7	14.2 2.1	14.3 2.1
Spleen	2.79 0.65	3.24 0.75	2.53 0.44	2.79 0.43	2.86 0.62	3.24 0.75	3.45 0.73	3.46 0.56	3.34 0.76	3.33 0.40
Liver	54.7 6.9	57.1 6.9	54.2 5.8	58.0 5.2	60.7 3.4	49.7 4.9	53.6 2.1	57.2 7.4	54.3 4.2	54.6 9.3
Brain	12.4 1.0	12.4 1.0	12.8 1.4	13.5 0.8	13.3 1.0	16.6 1.6	16.0 2.4	15.9 1.6	17.4 1.5	17.3 1.5
Gonad	6.71 0.70	6.71 0.80	6.93 1.07	7.17 0.83	6.65 0.79	0.48 0.22	0.69 0.23	0.61 0.38	0.83 0.42	0.71 0.32
Adrenal	0.18 0.06	0.18 0.02	0.25 0.14	0.29 0.14	0.28 0.12	0.27 0.06	0.38 0.13	0.32 0.13	0.52 0.28	0.52 0.17
Heart	4.79 0.63	4.68 0.42	4.89 0.25	5.19 0.45	5.59 0.44	4.55 0.40	4.05 0.48	4.65 0.52	5.03 0.39	5.27 0.43

Fig. 1. Correlation chart between heart weights and body weights in wild mice trapped at 1,400 m altitude (●) and laboratory mice reared at sea level (○).

Fig. 2. Relationship between the organ weight per body weight (%) and altitude (km) at the eleventh week after birth. (○ male, ● female, $M \pm S.D.$). The hatchings indicate the significant differences.

The Table 1 shows the organ weights at the eleventh week after birth, one week after the mice had been returned from the experimental stations to sea level. No differences are recognized in body weights at the third week after birth before exposure, in any groups and

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sexes. Sexual differences appeared clearly at the eleventh week after birth after exposure, but differences among the altitudes are not significant. The relationship between the organ weight per body weight ($\%$) and the altitude is illustrated in Fig. 2. Changes of the organ weights caused by the high altitude exposure are seen in the kidney (in male), the adrenal gland (in female) and the heart (in both sexes). These changes appeared over 2,000 m above sea level which is a very important phenomenon. This result is the same as for wild mice^{15,16}. The high mountain disease of cattle is not found under 7,000 ft (2,100 m) above sea level¹².

When the rat was exposed at 3,450 m, the body weight decreased at the initial stage, but thereafter it increased. The length of the period reduced body weight increased with age and body weight. Therefore the duration of decreasing period of the body weight was evaluated as a parameter of adaptability to the high altitude environment¹⁷. In several works, it was reported that the testis and ovary weight per body weight decreased when the rat was exposed to a 25,000 ft (7,500 m) simulated altitude¹⁸, and there was a significant reduction in rate of reproduction although there were no structural alteration in the primary sex organs when the rat was exposed to an 18,000 ft (5,400 m) simulated altitude¹⁹. A prolonged sojourn of the rat at a 3,450 m altitude did not have any undesirable influence on their growth or ovarian cycle²⁰. In studies of the breeding performance of *Sonoran deer mice* maintained for two years at an altitude of 3,800 m, the F2 litter size at the high altitude was smaller in number than that at sea level because the incidence of cannibalism of newborn litters at the altitude was much greater than that at sea level²¹. When the guinea pig was exposed for twenty minutes per day at an 14,000–18,000 ft (4,200–5,400 m) simulated altitude, heart and kidney weight per body weight increased²². After 35-day old rats born at sea level were transferred for ten months to an altitude of 12,470 ft (3,700 m), the weights of their heart and adrenal gland increased, and especially in F2, the cardiac hypertrophy was remarkable²³. Rat, mouse, guinea pig and rabbit were exposed to altitudes of 4,700 m above sea level, liver damage was observed and the body weight decreased²⁴.

Judging from these reports and the results obtained here, the extent of reaction will differ depending on the altitude, but it is presumed that the critical altitude for these reactions is about 2,000 m above sea level. No dysfunction was observed until 2,600 m in altitude, but because of the incidence of functional disorders, it was possible that a threshold pressure

Fig. 3. Several patterns of reaction in heart weight per body weight, caused by the sensitivity of litters. (No. 3, 6, 9 indicate the litter numbers)

Fig. 4. Body weights and organ weights per body weights (%) of male (○) and female (●) mice at the eleventh, fifteenth and twenty-second weeks after birth. (M±S.D.)

existed for acclimatization of the living body²⁵⁾. Under 2,600 m above sea level, as shown in Fig. 3, several patterns of reaction were recognized in the exposed mice, caused by the sensitivity of litters. Based on the fact that the heart weight increased in proportion to the altitude¹⁸⁾, reactions under 2,000 m above sea level should be studied in more detail.

During one, five and twelve weeks after returning to sea level from altitudes of 770 m and 1,400 m, the body weight of exposed female mice increased more than at sea level as time went on, as shown in Fig. 4. Adrenal gland weight of female mice exposed to high altitudes was much higher than that at sea level at the eleventh week after birth, but at the fifteenth or twenty-second week after birth, these differences disappeared. This indicates that the adrenal gland weight increase in exposed mice is reversible. It has been reported that changes in adrenal gland and thymus weight in rats maintained at 3,800 m altitude for ten months are reversible, but the cardiac hypertrophy of these rats is a permanent change²⁶⁾. Therefore, it may be interpreted that the alteration of the heart is different from that of the adrenal gland. The morphological and functional alterations of the heart in these individuals will be discussed in detail in the next report.

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高海拔環境曝露によるマウス臓器重量の変化

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平地で生産した ICR-JCL 系マウスを, 生後 3 週令で離乳, 無作為的に 5 群に区分し, 海拔の異なる 5 カ所 (平地, 770 m, 1,400 m, 2,000 m, 2,600 m) に配置して 10 週令までの 7 週間に亘って飼育した。10 週令で平地に回収, 生後 11 週令, 15 週令および 22 週令で剖検し, 脳, 心, 肝, 腎, 脾, 副腎および生殖腺の重量を計測, 分散分析法により, 高海拔環境曝露の影響を観察した。結果はつぎのとおりである。

1) 平地へ回収後 1 週間を経過した生後 11 週令では,

海拔 2,000 m 以上で飼育されたマウスの心 (雌雄), 副腎 (雌), 腎 (雄) の重量が増加する。2) 曝露による心重量の増加は, 母マウスによって反応のパターンが相違し, 感受性の差によると考えられる。3) 育成期を高海拔環境下で経過したマウスは, 平地へ回収後に増体量を増し, とくに雌では, 平地で飼育されたものと比べ, 生後 22 週令で明瞭な差が生ずる。4) 曝露による副腎重量の増加は, 平地へ回収後短時間の間に消退し, 心重量の増加とは様相を異にする。