NATURAL ACCLIMATIZATION TO HIGH ALTITUDES: ENDOCRINE FACTORS

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Prepared by Dr. Federico Moncloa, Instituto de Investigaciones de la Altura, Universidad Peruana Cayetano Heredia, Lima, Perú.
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INTRODUCTION

The present paper presents a review of the findings in high altitude natives (HAN) as compared with sea level natives (SLN) in regard to endocrine physiology obtained from work done in our laboratory and that reported in the literature.

MATERIAL AND METHODS

We have studied men born over 10,000 feet above sea level and living for more than a year either in Morococha (14,900 feet) or in Cerro de Pasco (14,000 feet). Our controls have been sea level native residents of similar age. The methods have been previously described (9-12).

ADRENAL CORTEX

The physiology of the human adrenal cortex has been explored in HAN by several investigators (3, 11, 12, 15, 18).

The urinary excretion of 17,21-dihydroxy-ketosteroids (17-OHCS) and 17-ketogenic steroids (17-KGS) has been found within the normal range (3, 11, 12, 18). These results are in accord with a normal cortisol secretion rate and with a normal plasma cortisol concentration (see Table 1). These last two findings allow us to state that the metabolic clearance rate (MCR) is the same in both populations. Using the formulae recommended by Tait (20): MCR = Cortisol secretion rate/Plasma cortisol concentration; we have that in high altitude native the MCR is 176.6 1/24 hrs. and 162.3 1/24 in sea level natives. This is reinforced by our observation that the amount of 17-OHCS appearing in the urine after the intravenous
injection of 100 mg of cortisol, was the same in HA and in SLN (12).

The interrelationship between the hypophysis and the adrenal cortex has been studied by us and others (3, 11, 18). The response of HAN and SLN to dexamethasone inhibition (12) and the methopyrine test (11) was similar. The stimulation with adrenocorticotrophin (ACTH) gave interesting results. When the dose used is in excess of the amount capable of eliciting maximal stimulation, HAN behave as SLN (3, 11); but with small doses, such as 1, 2 or 5 U, HAN have a lower response to ACTH in terms of the urinary excretion of 17-OHCS and 17 ketosteroids (17 KS) (11, 18). The explanation postulated for this observation is that ACTH has a faster catabolism in HAN. In favor of this hypothesis we have the results shown in Fig. 1. After a single intravenous injection of ACTH the time at which the plasma cortisol concentration starts to fall depends on the ACTH concentration (6). If the amount of ACTH injected is the same in both groups and if in a group the cortisol starts to fall down earlier, this should indicate that ACTH concentration is falling at a faster speed in such group. After the intravenous injection of 0.25 U of ACTH per Kg of body weight; HAN have their maximal cortisol concentration in 120 minutes and SLN have it at 135 minutes.

Further experiments are being made trying to settle this point. An alternative explanation could be a lower sensitivity of the adrenal cortex to ACTH.

THYROID

The thyroid is one of the main regulators of oxygen consumption and its physiology depends upon iodine metabolism. The relationship between
hypoxia and thyroid physiology has been investigated in acute hypoxia and in experimental animals. However, little information is available in chronic hypoxia, except the knowledge that the basal metabolic rate is normal (7) or slightly increased (13); that endemic goiter is seldom found in high altitude (2, 4) and that iodine disappearance from the iodine space is slower in the HAN than in SLN (9).

The plasma disappearance curve of $^{131}$I is illustrated in Fig. 2. The curve which corresponds to the high altitude group has a less pronounced slope than that of the sea level group. The biological half-life in the high altitude group is of 3.8 hrs. and in the sea level group of 3.1 hrs. The results of the urinary excretion are represented in Fig. 3, in which can be seen that HAN excrete a smaller proportion of the $^{131}$I dose, the difference between this two groups have a statistical significance, being in all cases $P$ less than 0.01. The thyroidal uptake is shown in Fig. 4. The high altitude group, because of the results of the urinary excretion as by the shape of the curve of thyroidal uptake and of the values it reaches, resembles what is expected to be found in situations of iodine deficiency (14, 17). However, the disappearance curve of $^{131}$I, rules out a lower iodine intake as the only explanation. In iodine deficiency the biological half-life is lower than the one found in normals (14) which was not the case in HAN.

The results of a high uptake at 24 hours, which is accompanied by a curve of disappearance of $^{131}$I delayed, suggest that the clearance of the isotope from the blood is diminished; this seems to be the case of the HAN. The decrease in the renal excretion of iodine could be the cause for iodine remaining longer in its space, and this would cause secondarily a greater percentual thyroidal uptake.
The explanation for the lower renal excretion is not easy, it is likely that the lower renal plasma flow, described in the HAN, (1, 8) may be one cause, other possibility could be that the red blood cells, which we know are increased in the HAN (22), act like iodine reservoirs. A third interpretation may be a slower diffusion of iodine from plasma to the extra and intra cellular fluids. Even though our results do not allow us to disregard completely the lack of iodine as one of the factors which can explain our findings in HAN, one is tempted to speculate that either deficient elimination or slow diffusion of iodine would result in the requirements for this element being lower (14); if that is the case, one could offer this as an explanation for the lower incidence of endemic goiter in the highest altitudes (2, 4, 9).

GONADS
Not too many studies have been made in regard with gonadal function in HAN, Guerra-García et al (5) have reported that the urinary excretion of testosterone in men was 96.5 µg/24 hrs, a very similar value to what was founded in SLN; 99.8 µg/24 hrs. Sobrevilla et al. have reported no difference in total urinary gonadotrophins (16). However, Guerra-García (personal communication) has done some observations in the urinary excretion of testosterone under stimulation with human chorionic gonadotrophins. His results indicate a lower and shorter increase in the HAN, resembling what happens with the corticoids response to ACTH stimulation.

CATECHOLAMINES
The plasma levels of adrenaline and noradrenaline have been found, in
fasting conditions, to be 0.07 μg/l and 0.36 μg/l in HAN as compared with 0.03 μg/l and 0.33 μg/l in SLN (10). The differences were not statistically significant. Under hypoglycemia, caused by insulin injection, a raise in adrenaline is observed in both populations. However, the figures in HAN were significantly higher than in SLN (see figure 4). The glycemic recovery starts in HAN from a lower concentration but is of the same magnitude than in SLN. The more intense hypoglycemia would explain the greater adrenaline concentrations; but the fact that the recovery was the same, despite the higher adrenaline concentration may be interpreted as some sort of "resistance" to adrenaline. A decreased action of adrenaline under hypoxia has been described by other investigators (19, 21).

SUMMARY

The results presented indicate that most of the endocrine indexes are within normal range in the HAN. However, there is evidence that under certain circumstances the HAN has a lower response to several hormones.
REFERENCES


Table 1.— Urinary excretion of some steroids, cortisol secretion rate and plasma cortisol concentration in high altitude and sea level natives.

<table>
<thead>
<tr>
<th></th>
<th>Sea level mean ± SE</th>
<th>High altitude mean ± SE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urinary 17-OHCS</strong></td>
<td>6.2 ± 0.3 (10)</td>
<td>5.4 ± 0.5 (10)</td>
<td>3</td>
</tr>
<tr>
<td>mg/24 hrs</td>
<td>6.5 ± 0.4 (21)</td>
<td>5.7 ± 0.3 (15)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>6.2 ± 0.3 (42)</td>
<td>5.5 ± 0.2 (28)</td>
<td>11</td>
</tr>
<tr>
<td><strong>Urinary 17-KGS</strong></td>
<td>15.8 ± 1.2 (15)</td>
<td>14.3 ± 0.9 (10)</td>
<td>11</td>
</tr>
<tr>
<td>mg/24 hrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cortisol Secretion Rate</strong></td>
<td>18.8 ± 1.4 (7)</td>
<td>16.7 ± 1.4 (10)</td>
<td>11</td>
</tr>
<tr>
<td>mg/24 hrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plasma cortisol</strong></td>
<td>11.6 ± 0.7 (20)</td>
<td>9.5 ± 0.9 (16)</td>
<td></td>
</tr>
<tr>
<td>ug/100 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The figures in parenthesis are the number of determinations.

The differences are not statistically significant.
Table 2.- Urinary 17-OHCS (mg/24 hrs) under Dexamethasone, methopyrapone and ACTH tests in high altitudes and sea level natives.

<table>
<thead>
<tr>
<th></th>
<th>Sea level mean ± SE</th>
<th>High altitudes mean ± SE</th>
<th>P values</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH 1 u</td>
<td>14.7 ± 0.8 (20)</td>
<td>11.5 ± 0.8 (15)</td>
<td>&lt; .01</td>
<td>11</td>
</tr>
<tr>
<td>ACTH 2 u</td>
<td>15.3 ± 1.0 (21)</td>
<td>11.0 ± 1.0 (15)</td>
<td>&lt; .01</td>
<td>18</td>
</tr>
<tr>
<td>ACTH 5 u</td>
<td>23.3 ± 1.2 (21)</td>
<td>16.9 ± 1.5 (15)</td>
<td>&lt; .01</td>
<td>18</td>
</tr>
<tr>
<td>ACTH 20 u</td>
<td>20.2 ± 1.3 (11)</td>
<td>18.8 ± 1.1 (13)</td>
<td>N.S</td>
<td>11</td>
</tr>
<tr>
<td>ACTH 25 u</td>
<td>15.1 ± 0.7 (10)</td>
<td>14.0 ± 0.9 (10)</td>
<td>N.S</td>
<td>3</td>
</tr>
<tr>
<td>Methopyrapone</td>
<td>17.9 ± 1.8 (10)</td>
<td>14.9 ± 2.1 (7)</td>
<td>N.S</td>
<td>11</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1.4 ± 0.1 (10)</td>
<td>1.2 ± 0.2 (13)</td>
<td>N.S</td>
<td>12</td>
</tr>
</tbody>
</table>

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LEGENDS OF FIGURES

Fig. 1.- Plasma cortisol concentration after a single intravenous injection of ACTH (0.25 u/Kg).

Fig. 2.- Plasma I-131 disappearance curve intravenous injection.

Fig. 3.- Urine I-131 accumulated excretion intravenous injection.

Fig. 4.- Thyroidal uptake.

Fig. 5.- Plasma adrenaline in fasting and hypoglycemia in high altitude and sea level natives.
PLASMA 1-131 DISAPPEARANCE CURVE
INTRAVENOUS INJECTION

MEAN ± S.E.

HIGH ALTITUDE

SEA LEVEL

% OF DOSE/LITER

HOURS

FIG. 2

URINE 1-131 ACCUMULATED EXCRETION
INTRAVENOUS INJECTION

MEAN ± S.E.

HIGH ALTITUDE

SEA LEVEL

% OF DOSE

HOURS

FIG. 3
TIME IN HOURS

THYROIDAL UPTAKE
MEAN ± SE

% OF DOSE

○ SEA LEVEL
■ HIGH ALTITUDE

TIME IN MINUTES

PLASMA ADRENALINE IN FASTING AND HYPOGLUCEMIA IN HIGH ALTITUDE AND SEA LEVEL NATIVES

GLUCOSE SEA LEVEL
GLUCOSE HIGH ALTITUDE
ADRENALINE SEA LEVEL
ADRENALINE HIGH ALTITUDE

FIG. 4

FIG. 5