AD-A142 791 ENDOGENOUS OPIOIDS AND VENTILATORY ADAPTATION TO PROLONGED HYPOXIA IN GOATS(U) ARMY RESEARCH INST OF ENVIRONMENTAL MEDICINE NATICK MA S E WEINBERGER ET AL. 1/1

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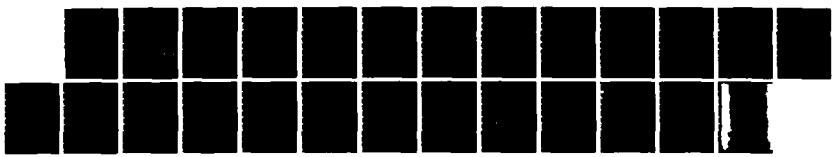

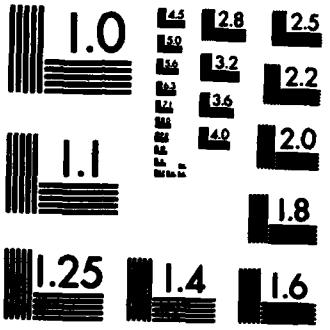

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To investigate whether endogenous opioid peptides mediate time-dependent changes in arterial PCO_2 and ventilatory responsiveness during prolonged hypoxia, we studied four goats at rest during 14 days in a hypobaric chamber (~~P_B = 450 Torr~~). Arterial PCO_2 fell during the first several hours of hypoxia and then remained stable over the next 7 days. By day 14, $PaCO_2$ rose somewhat, and ventilatory responsiveness to CO_2, while still greater than normal, was less than that observed over the first week of hypoxia. Immunoactive β-endorphin levels in plasma and CSF did not change during the 14-day period. Administration of naloxone on day 14 did

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did not restore the ventilatory response to CO_2 to the level observed during the earlyphase of acclimatization. We conclude that, in goats: (1) time-dependent changes in resting arterial PCO2 during acclimatization to prolonged hypoxia are associated with reciprocal changes in the ventilatory response to CO_2; and (2) these changes in resting $PaCO_2$ and ventilatory responsiveness are not associated with or attributable to alterations in endogenous opioid peptide levels in plasma or CSF.

ENDOGENOUS OPIOIDS AND VENTILATORY ADAPTATION TO PROLONGED HYPOXIA IN GOATS

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ABSTRACT

To investigate whether endogenous opioid peptides mediate time-dependent changes in arterial PCO_2 and ventilatory responsiveness during prolonged hypoxia, we studied four goats at rest during 14 days in a hypobaric chamber (P_B~450 Torr). Arterial PCO_2 fell during the first several hours of hypoxia and then remained stable over the next 7 days. By day 14, $PaCO_2$ rose somewhat, and ventilatory responsiveness to CO_2, while still greater than normal, was less than that observed over the first week of hypoxia. Immunoactive β-endorphin levels in plasma and CSF did not change during the 14-day period. Administration of naloxone on day 14 did not restore the ventilatory response to CO_2 to the level observed during the early phase of acclimatization. We conclude that, in goats: 1) time-dependent changes in resting arterial PCO_2 during acclimatization to prolonged hypoxia are associated with reciprocal changes in the ventilatory response to CO_2; and 2) these changes in resting $PaCO_2$ and ventilatory responsiveness are not associated with or attributable to alterations in endogenous opioid peptide levels in plasma or CSF.

Index terms: Endorphins, naloxone, altitude, ventilatory acclimatization, CO_2 response curves

Introduction

Ventilatory adaptations to chronic hypoxia have been well described in a number of species (6). The initial response to hypoxia, characterized by a fall in arterial PCO_2, is followed within hours to days by a further decrement in arterial PCO_2 called "short-term acclimatization". Mechanisms postulated to explain short-term acclimatization have recently been reviewed in detail (6).

In some species, specifically ponies (18), goats (14), dogs (2), and cats (24), short-term acclimatization is followed within weeks by a return of arterial PCO_2 toward normal. This partial loss of the hyperventilation observed with short-term acclimatization is called "long-term acclimatization"; its mechanisms have yet to be elucidated.

We reasoned that the stress of chronic hypoxia might serve as a stimulus for increased activity of the endogenous opioid peptide system. Since these peptides have been shown to depress ventilation and ventilatory responsiveness when administered to experimental animals (7, 10, 16), we hypothesized that an augmentation of opioid peptide activity might be responsible for the process of long-term acclimatization. We studied the phenomenon of long-term acclimatization to hypoxia in goats, and tested our hypothesis by measuring β-endorphin immunoactivity in plasma and CSF in 4 animals during 14 days of sustained hypoxia. Additionally, we administered naloxone, an opiate antagonist, to see whether the manifestations of long-term acclimatization

could be reversed.

Methods

Four adult goats (mean body wt 40 kg, range 22 - 69 kg) were used for the study. Each goat was surgically prepared at least one month prior to study by creation of a skin-denervated carotid loop and by implantation of a guide tube through the occipital bone for convenient access to the cisterna magna and to cerebrospinal fluid (CSF) (9). At the start of each experimental day, a plastic cannula was inserted into the carotid arterial loop for continuous monitoring of heart rate and blood pressure, and for sampling of arterial blood. A needle was inserted through the guide tube into the cisterna magna for sampling of CSF.

All measurements were obtained with the goats in a chamber maintained under normobaric or hypobaric conditions, as specified by the protocol. For hypobaric conditions, the chamber was maintained at a pressure of 446±5 Torr, corresponding to an altitude of 4300 m. The chamber was monitored round-the-clock for pressure, temperature (maintained at 21 ±1° C), and composition of air. Chamber ventilation was adjusted so that the concentration of CO_2 within the chamber never exceeded 0.4%. While in the chamber, goats had free access to drinking water and salt licks and were fed regularly except for an overnight fast before each day of study.

Ventilatory responsiveness to CO_2 was tested by a

modification of Read's hyperoxic rebreathing method (20), described in detail previously (23). Rebreathing tests were performed in triplicate on each goat under each experimental condition.

Arterial PO_2, PCO_2 and pH were measured with a Radiometer blood gas analyzer (BMS3Mk2). Measurements were made at 37° C and corrected to rectal temperature of the goat at the time of sampling (11). Base excess or base deficit (±BE) was determined with a blood gas calculator (22).

For plasma immunoactive endorphin measurements, arterial blood was obtained at times specified in the protocol. Blood was drawn into a refrigerated plastic syringe, transferred to a chilled glass tube containing heparin, and centrifuged at 4° C (3000 rpm, 10-15 min). Aliquots of the plasma supernatant were transferred to 1.5 ml polypropylene tubes and then rapidly frozen in a dry ice-acetone bath before storage at -70° C. Cerebrospinal fluid (2 ml) was also drawn at specified times, rapidly frozen in dry ice-acetone, and stored at -70° C. Radioimmunoassay of plasma and CSF for β-endorphin immunoactivity was performed according to previously described methods (3,4), using duplicate samples of 50 and 300 microliters, respectively. All experimental samples were measured in the same assay, the sensitivity of which was approximately 60 pg/ml for plasma and 10 pg/ml for CSF.

Parallelism between the assay standard curves and binding curves using goat plasma extracts was demonstrated in

preliminary validation studies (data not shown). Gel permeation chromatography of similar extracts revealed that beta-endorphin immunoactivity in goat plasma reflected contributions from β-endorphin and its precursor β-lipotropin, consistent with previous studies in rats (1), sheep (3), and humans (4).

Protocol:

Goats were placed in the chamber, which was at normal barometric pressure, on day 0 and allowed 24 hours to adjust to the new environment. The following control data were collected on day 1 prior to decompression: 1) three hypercapnic rebreathing tests; 2) two samples of arterial blood during air breathing, for measurement of PO_2, PCO_2, and pH, one obtained before and one at least 20 minutes after the CO_2 rebreathing tests; 3) two samples of arterial blood for determination of β-endorphin immunoactivity, one before and one at least 20 minutes after the hypercapnic rebreathing studies; and 4) cerebrospinal fluid (CSF) for measurement of β-endorphin immunoactivity, obtained before the CO_2 rebreathing tests. The chamber was then decompressed over approximately 15 min to 446 Torr, simulating an altitude of 4300 m; goats were kept at that pressure for two weeks.

Blood was collected for measurement of β-endorphin immunoactivity at 15 min and at 1, 2, and 3.5 hr following arrival at altitude. Arterial blood gases were measured at 1 and 3.5 hr, and three CO_2 response tests were performed at 4 hr

after arrival at altitude.

On days 3, 7, and 14 at simulated altitude the following studies were done on each goat: 1) arterial blood was obtained for measurement of PO_2, PCO_2, and pH; 2) arterial blood and CSF were obtained for determination of β-endorphin immunoactivity; and 3) three CO_2 rebreathing tests were performed. On days 7 and 14, after the third rebreathing test, naloxone 10 mg was injected into the jugular vein. Three post-naloxone hypercapnic rebreathing tests were then performed on each goat, starting approximately 10 min after naloxone administration.

Data Analysis:

For each hypercapnic rebreathing test, minute ventilation ($\dot{V}E$) was calculated by computer on a breath-by-breath basis, expressed at BTPS conditions. Data from the triplicate rebreathing studies in each goat were pooled for statistical analysis. Linear regressions were calculated by the method of least squares for plots of $\dot{V}E$ as a function of simultaneously measured $PETCO_2$. Ventilatory responsiveness of each goat to CO_2 rebreathing was evaluated by determining the slopes of these lines, their intercepts on the $PETCO_2$ axis, and the calculated values of $\dot{V}E$ at $PETCO_2$ = 60 Torr. For control measurements of arterial blood gases and plasma β-endorphin levels, mean values of the two samples obtained from each goat were used.

Comparison of data obtained at multiple times was performed by analysis of variance (ANOVA) and by Newman-Keuls multiple

sample comparisons (25). The effect of naloxone on hypercapnic responsiveness at days 7 and 14 was determined by two-factor ANOVA. A p value <0.05 was considered statistically significant.

Results

The values of arterial blood gases obtained during normoxia and over the 14-day period of hypoxia are shown in Figure 1. Fig. Arterial PO_2 fell from a mean ($\pm$SD) control level of 94$\pm$ 2 Torr to a nadir of 35 $\pm$ 4 Torr after one hour at simulated altitude. The mean $PaCO_2$ fell from 36 $\pm$ 3 Torr at normoxia to 31 $\pm$ 2 Torr after 1 hr at altitude. At 3.5 hr, $PaCO_2$ was 27$\pm$3 Torr, and subsequently remained essentially stable through day 7. By day 14, the mean $PaCO_2$ had risen to 29 $\pm$ 3 Torr. During the first 3.5 hr after ascent to simulated altitude, arterial pH increased from 7.45 $\pm$ 0.03 to 7.49 $\pm$ 0.05. Throughout the next 14 days pH dropped continuously, reaching a value of 7.46$\pm$0.02 on day 14. Base excess was +1.5 $\pm$1.8 meq/L initially (during normoxia), and was -2.5$\pm$2.5 meq/L on day 7 and -1.3$\pm$2.3 meq/L on day 14 of simulated altitude.

Mean ($\pm$ SD) slopes, X-intercepts, and $\dot{V}E$ calculated at $PETCO_2$ = 60 Torr for the hyperoxic CO_2 rebreathing curves are shown in Figure 2. Before the goats were made hypoxic, the mean Fig. X-intercept was 55.6$\pm$5.5 Torr, with a slope of 4.1$\pm$2.0 L/min/Torr. Over the first 7 days at simulated altitude,

ventilatory responsiveness to hypercapnia progressively increased, as indicated by an increasing slope and a decreasing X-intercept. The maximum response was observed on day 7, and by day 14, ventilatory responsiveness was less than that observed on day 7. Mean ventilation at $PETCO_2$ = 60 Torr was 131.6 ± 27.2 L/min on day 7, and fell to 70.6 ± 5.3 L/min on day 14 ($p<0.001$) (Figure 2). No significant effect on hypercapnic ventilatory responsiveness was observed when naloxone (10 mg) was administered intravenously to the goats on days 7 and 14 (Table 1). Table

Measurements of immunoactive β-endorphin in plasma and CSF are shown in Figure 3. There was no statistically significant change in levels of either plasma or CSF β-endorphin, and no trends were observed. Fig. 3

As a positive control, to assure that the assay we used was capable of demonstrating changes in β-endorphin immunoactivity in goat plasma, we administered E. coli endotoxin (300 ng/kg) intravenously to 2 goats in a separate experiment, and measured their plasma endorphin levels over the following 2 hours (3). As shown in Figure 4, there was a marked, biphasic rise in plasma endorphin levels after endotoxin, one peak seen at 30 min and the other peak seen at 2 hrs following injection of endotoxin. Fig. 4

during asphyxia suppressed medullary respiratory activity. On the other hand, in adult humans, a rapid fall in ventilatory response to steady-state hypoxia occurs after an initial peak, and is not altered by administration of naloxone (13).

In this study, we were primarily interested in investigating long-term acclimatization to chronic hypoxia, i.e. the partial loss of resting hyperventilation observed during short-term acclimatization (6). We postulated that this change might be mediated by release of endogenous opioid peptides in response to prolonged hypoxia. The time course and even the existence of long-term acclimatization vary greatly from species to species; we chose to study goats, a species much used in altitude research and one in which the arterial PCO_2 has been shown to rise during the second week of hypoxia (14,15).

When exposed to prolonged hypoxia at simulated altitude, our goats demonstrated the phenomena of short-term and long-term acclimatization (6). On the basis of arterial PCO_2 measurements, short-term acclimatization was maximal between 3.5 hr and 7 d. Ventilatory responsiveness to hypercapnia was maximal at 7 d, as determined by the slope and position of the regression lines relating ventilation and $PETCO_2$, as well as by $\dot{V}E$ at $PETCO_2$ = 60 Torr. Between days 7 and 14 of hypoxia, resting arterial PCO_2 rose somewhat from the lowest value, and the position and slope of the ventilatory response line shifted back towards those obtained under control normoxic conditions.

Lahiri, et al. (14) observed the rise in arterial PCO_2 with

long-term acclimatization in goats and attributed it to augmented production of CO_2 by the rumen of the goat during chronic hypoxia. Since our data show that the increased PCO_2 was accompanied by a decrease in ventilatory responsiveness to hypercapnia, it seems more likely that a decrement in ventilatory responsiveness was responsible for the rise in $PaCO_2$. The same investigators (15) later proposed that, with prolonged hypoxia, partial non-respiratory compensation for metabolic acidosis in the central nervous system acts to decrease ventilatory drive and to condition longterm ventilatory acclimatization during chronic hypoxia. Our data do not directly address the validity of the latter hypothesis.

We found no evidence to suggest that the endogenous opioid peptide system plays an important role in long-term acclimatization to hypoxia in goats. Levels of β-endorphin immunoactivity remained stable both in plasma and in cisternal fluid over the 14-day period of hypoxia. We cannot completely exclude the possibility that endogenous opioid activity is altered during chronic hypoxia, since local tissue changes of opioid peptides acting as neurotransmitters would not necessarily be reflected by either plasma or cisternal fluid levels, and since our radioimmunoassay does not measure levels of enkephalins or dynorphin. However, failure of naloxone to increase significantly hypercapnic responsiveness on day 14 also suggests that opioids are not primarily responsible for partial loss of ventilatory responsiveness during long-term

acclimatization.

We demonstrated a marked rise in plasma β-endorphin immunoactivity in two goats following administration of endotoxin, with a bi-modal peak identical to that found in a previous study in sheep (3). Thus, our assay system readily measured increments in β-endorphin immunoactivity following a known stimulus for β-endorphin release.

We conclude that the phenomenon of long-term acclimatization to hypoxia in goats can be shown after two weeks by both a rise in resting $PaCO_2$ and a decrease in ventilatory response to hypercapnia, compared with the values obtained during short-term acclimatization. Unchanged β-endorphin immunoactivity in plasma and cisternal fluid during this time, along with failure of naloxone administration to restore the high hypercapnic ventilatory responsiveness, strongly suggest that endogenous opioid peptides do not modulate the changes of long-term acclimatization to hypoxia in goats.

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The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation. In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

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TABLE 1. Hypercapnic ventilatory responsiveness after 7 and 14 days at simulated altitude: minute ventilation (L/min, BTPS) at $PETCO_2$ = 60 Torr before and after naloxone injection (N).

	Day 7		Day 14	
Goat	Before N	After N	Before N	After N
1	165	167	71	73
2	108	108	78	105
3	111	121	67	95
4	142	104	66	61
Means	132	125	71	84
(SD)	(27)	(29)	(5)	(20)

The effect of time is statistically significant ($p \leq 0.001$).
There is no statistically significant effect of naloxone or interactive effect between naloxone and time (2-way ANOVA).

FIGURE LEGENDS

FIG. 1. Mean (± SD) values for arterial PO_2, PCO_2, pH, and base excess (BE) during 2 weeks at simulated altitude (4300 m). C = normoxic control data, obtained before the pressure in the chamber was lowered. Statistically significant differences between sequential measurements (by Newman-Keuls multiple sample comparisons) are noted on the line connecting the sequential mean values. **P<0.001. *P<0.05.

FIG. 2. Mean (±SD) values for intercept, slope, and $\dot{V}_E$ at $PETCO_2$ = 60 Torr characterizing the hypercapnic response curves during 2 weeks at simulated altitude. C = normoxic control data, obtained before the pressure in the chamber was lowered. Statistical significance of differences between sequential measurements is noted on the line connecting the sequential mean values. **P<0.001. *P<0.05. +0.05<P<0.10

FIG. 3. Mean (± SD) levels of immunoactive β-endorphin in plasma and CSF during 2 weeks at simulated altitude. C = normoxic control data, obtained before the pressure in the chamber was lowered. No statistically significant changes over time (ANOVA).

FIG. 4. Immunoactive plasma endorphin levels in 2 goats following intravenous administration of E. coli endotoxin. C = control, before injection of endotoxin.

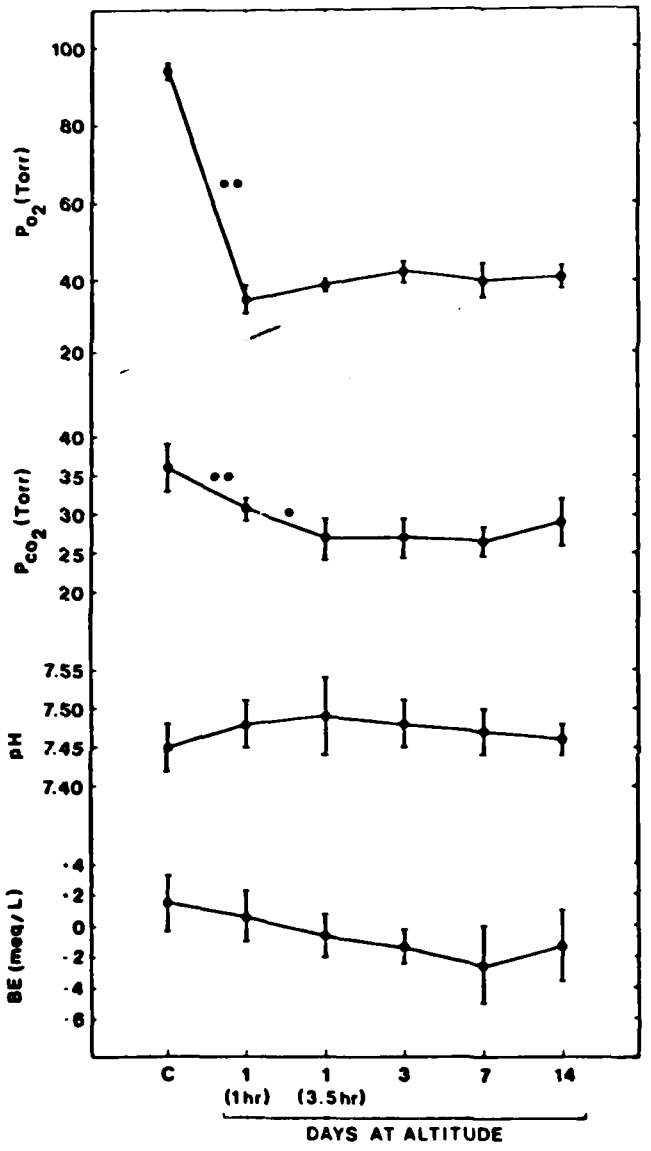
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Figure 1

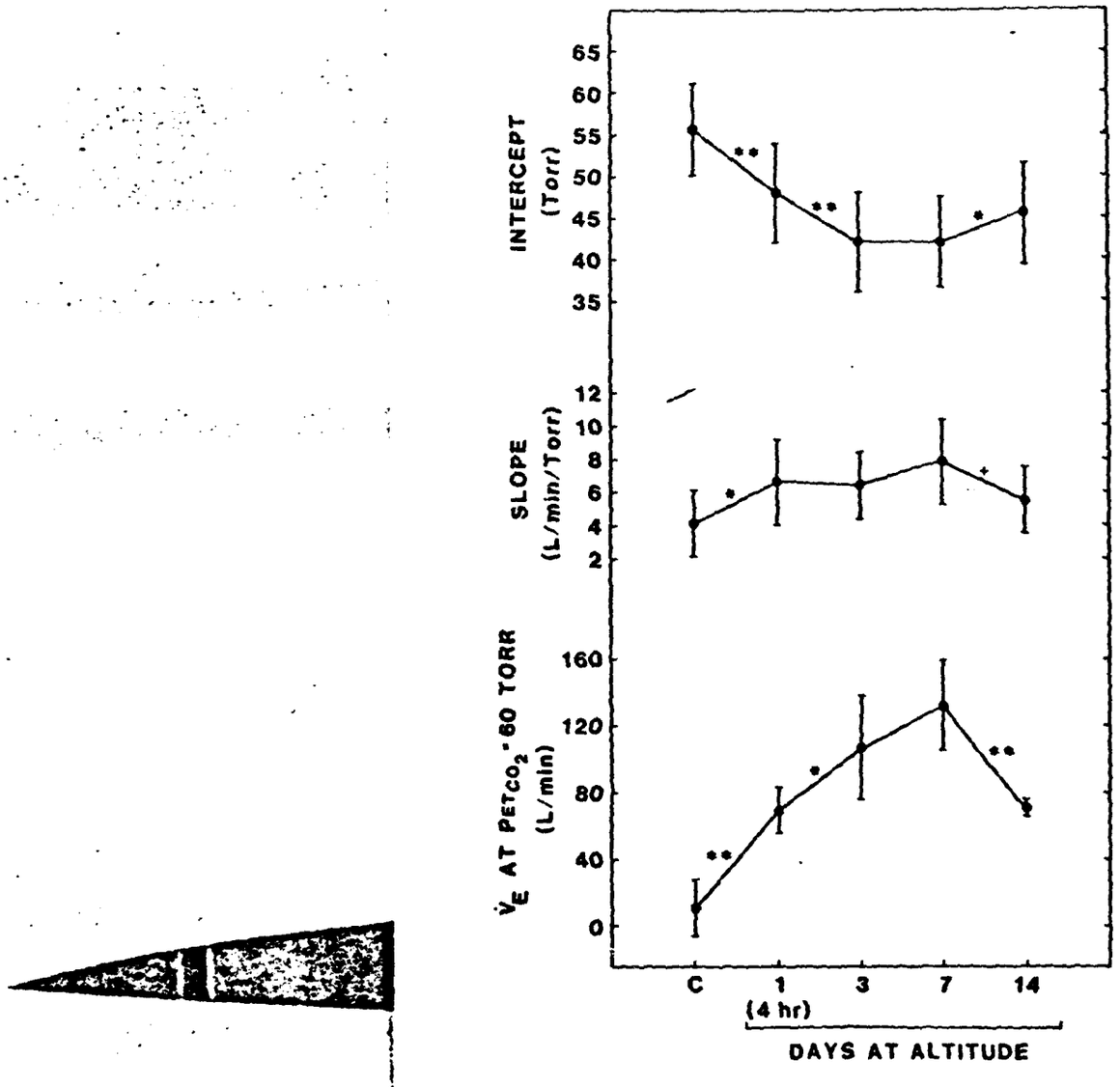
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Figure 2

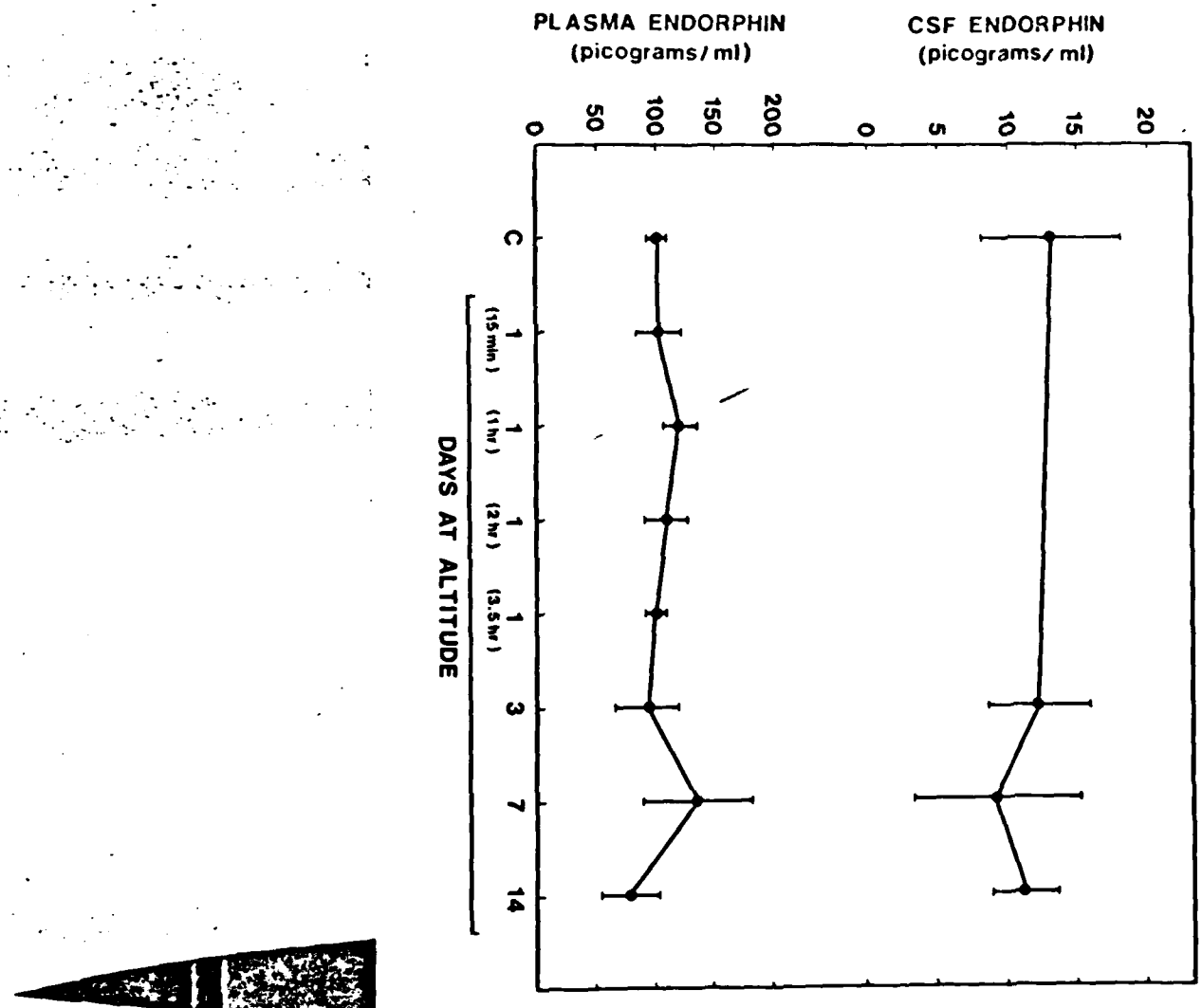
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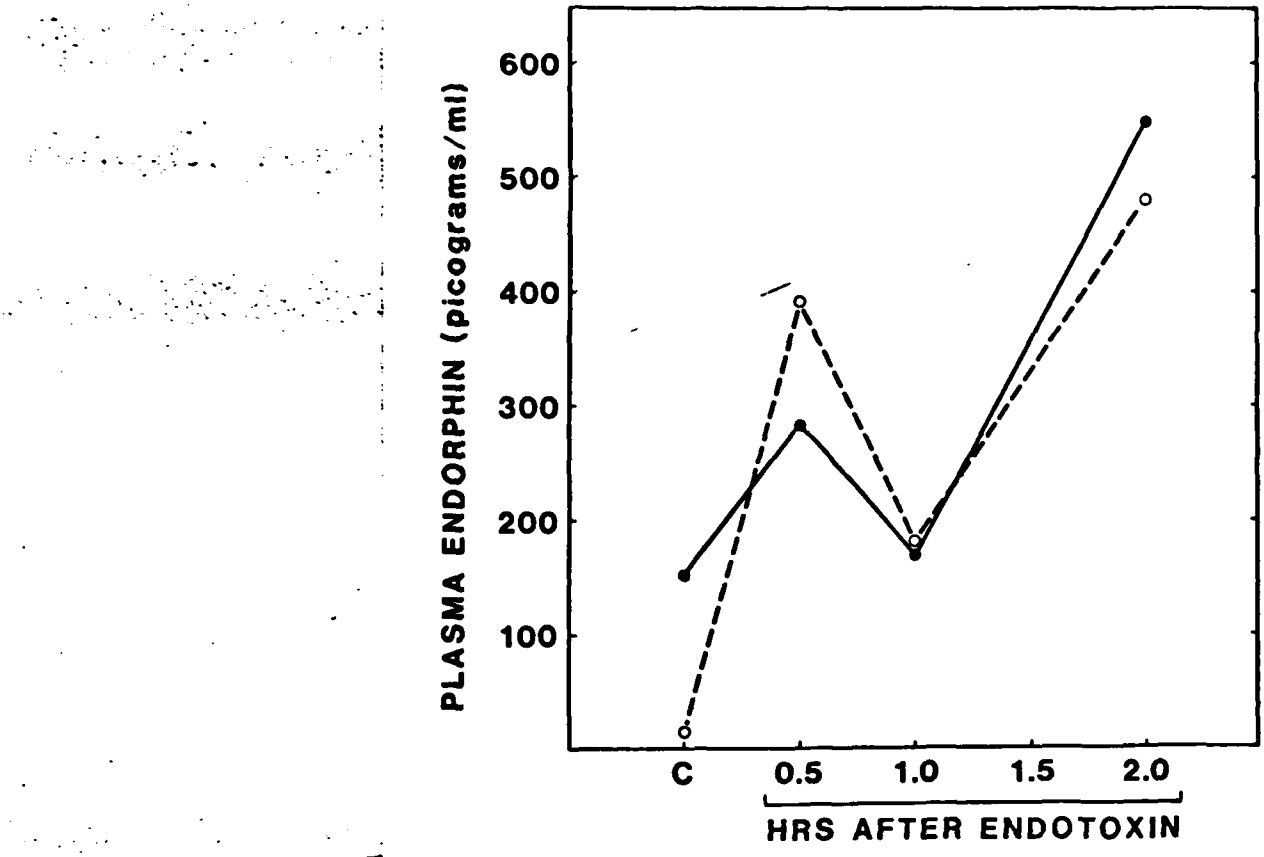
Figure 3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100
C
0.5
1.0
1.5
2.0
HRS AFTER ENDOTOXIN

Figure 4