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HIGH ALTITUDE EXPOSURE ON BODY WEIGHT IN MALE RATS: EFFECT OF CYPROHEPTADINE

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SUMMARY. The role of 5-hydroxytryptamine (5-HT), as mediator of body weight changes during high altitude exposure was investigated in male rats using cyproheptadine, a 5-HT antagonist. At sea level male rats daily injected with either 10 mg/kg of cyproheptadine chlorhydrate or saline solution showed no differences in body weight after five days of treatment. Other rats were acutely exposed to an altitude of 4,338 m. and they were daily injected with either cyproheptadine or the vehicle. Rat weight was recorded daily during four days. Through the first and second days of exposure, a similar reduction in body weight was observed in both groups. After three days of exposure at high altitude, cyproheptadine-treated group decreases body weight to a lesser extent than the control group. Between the third and fourth days of permanence at high altitude a gain of weight only occurred in the cyproheptadine treated group. Since cyproheptadine and saline treated groups at sea level showed the same pattern of weight curves whereas hypoxic male animals cyproheptadine-treated group had a better weight than those obtained in saline treated group, it is suggested that 5-HT may be mediating body weight reduction during high altitude exposure of male rats.

RESUMEN. Se ha investigado el rol de la serotonina como mediador de los cambios en el peso corporal de ratas machos tratadas con ciproheptadina y expuestas agudamente a la altura. A nivel del mar las ratas tratadas con 10 mg/kg de ciproheptadina o con solución salina no mostraron cambios en el peso corporal después de 5 días de tratamiento. Otro grupo de ratas fueron expuestas agudamente a una altura de 4338 m y fueron inyectadas diariamente con ciproheptadina ó el vehículo. El peso de las ratas fué registrado diariamente durante 4 días. Al primer y segundo día de exposición se observó una reducción del peso corporal de similar magnitud en ambos grupos (tratado y control). Al tercer día de exposición el grupo tratado con ciproheptadina disminuyó el peso coporal en una menor magnitud que el grupo control. Entre el tercer y cuarto día de permanencia en la altura se observó una ganancia del peso corporal sólo en el grupo tratado con ciproheptadina. Dado que los grupos tratados con ciproheptadina y solución salina (control) a nivel del mar mostraron el mismo patrón de curvas de peso corporal, mientras que en la altura, las ratas tratadas con ciproheptadina tuvieron un mejor peso que las obtenidas con solución salina, se sugiere que la serotonina estaría mediando la reducción del peso corporal durante la exposición a la altura.

INTRODUCCION

In the living organisms submitted to hypobaric hypoxia, different tissues and systems are involved in the processes of adaptation resulting in a minor growth than those observed at sea level. This is confirmed in men (1), rats (2) and guinea-pigs (3). The influence of neurotransmitters on these processes have been only partially studied.

On the other hand, it has been shown that 5-hydroxytryptamine (5-HT) may modulate systems regulating body weight (4), intake of protein (5) or the relative proportions of protein and carbohydrates (6). Furthermore, a treatment of 20 mg/kg/day during 5 days of 5-HT produces a decrease in body weight of male rats (7).

This report characterizes the role of 5-HT in modulating body weight in male rats exposed to high altitudes using cyproheptadine chlorhydrate, a 5-HT antagonist.

MATERIAL AND METHODS

Animals. 56 male rats of the holtzman strain were used for this study. They were grouped as follows:

a) Sea level-control group (SLCG).
b) Sea level-cyproheptadine-treated group.
c) High altitude (4,338 m.) exposure-group (HAEG).
d) High altitude exposure-cyproheptadine-treated group.

They had free access to food and water. A 12/12 hour light-dark cycle was used.

During 5 days in the SLCG, 5 rats were injected intra-peritoneally with 10 mg/kg of cyproheptadine chlorhydrate (a gift from Merck, Sharp & Dohme, Peruana) and other 3 rats with saline vehicle.

Twenty four rats of the HAEG were injected with 10 mg/kg of cyproheptadine chlorhydrate the day before traveling to Cerro de Pasco, Perú (4,338 m.) and the next four days. A similar number of rats were used as control group in HAEG.

The trip lasted 10 hours. The departure was at 8:30 p.m. Two hours later the bus traveled at altitudes over 3,000 m. We, therefore, considered that the exposure to high altitude began the day of departure at 10:30 a.m. Rats were housed in our laboratory in the High Altitude Institute, at Cerro de Pasco and maintained at 15° C room temperature.

Weight Recording

Individual weight of the previously identified rats was recorded daily. Weights were always measured at about 11 a.m. in an animal balance having an error of ± 1 g.

Calculations

Experimental weight data of the different groups were tested by using one.way analysis of variance. The significance of the differences between the individual means was assessed with Duncan's multiple test.

RESULTS

Analysis of data in male rats exposed to 4,338 m. altitude during four days showed a marked loss in body weight.

It can be seen that body weight of mature male rats submitted to hypoxia are statistically different from those of control at sea level on the third and fourth days of exposure (Table 1).

Table 1. Body Weight in Male Rats during Exposure to High Altitude (4,338 m).

Days	Sea level*	4,338 m. *	P
0	255.3 ± 22.1	243.0 ± 7.5	NS
1	257.8 ± 21.8	232.1 ± 6.9	NS
2	260.6 ± 22.4	228.9 ± 6.8	NS
3	264.6 ± 21.8	222.0 ± 6.1	0.05
4	269.7 ± 20.6	222.3 ± 5.8	0.02

* Values are means ± S.E.M. (gr.)

In Table 2 may be observed the effect of cyproheptadine on body weight of male rats. The injections of cyproheptadine chlorhydrate to male rats were able to prevent the differences in body weight due to hypoxia which it was observed in the group receiving vehicle alone. This effect of cyproheptadine was not observed at sea level (Table 3).

Table 2. Body Weight in Male Rats during Exposure to High Altitude. Effect of Cyproheptadine (10mg/kg BW).

Days	Sea level *	4 ,338 m. *	P
0	255.9 ± 19.5	231.2 ± 8.9	NS
1	256.7 ± 19.4	221.1 ± 8.3	NS
2	257.7 ± 19.5	216.7 ± 8.2	NS
3	253.5 ± 19.6	213.5 ± 8.1	NS
4	251.0 ± 19.9	217.4 ± 7.6	NS

* Values are means ± S.E.M. (gr.)

Table 4 shows the daily body weight variation. During the first and second days at 4,338 m. altitude, a body weight reduction was observed. This was similar in both saline treated- HAEG and high altitude exposure-Cyproheptadine treated group. Between the second and third days, the reduction of weight in saline treated-HAEG increased (-6.96 grs.) whereas in the high altitude exposure-Cyproheptadine treated group only a slight decrease of weight was observed (-3.02 gr.) ($P < 0.01$). Between the third and fourth days of exposure at high altitude a gain of weight occurred only in the high altitude exposure-cyproheptadine treated group ($P < 0.02$).

Table 3. Body Weight Variation in Male Rats treated with Cyproheptadine (10mg/kg BW).

Days	Control		Cyproheptadine	
	⌂ X	SEM	⌂ X	SEM
0-1	2.5	0.3	0.8	0.2
1-2	5.3	0.3	1.6	0.2
2-3	9.3	0.3	-2.4	3.0*
3-4	14.4	1.4	-4.9	4.3**

* Different from control at $P < 0.01$

Table 4. Body Weight Variation in Male Rats during Exposure at High Altitude.

Days	Saline Treated HAEG		Cypro Treated HAEG	
	⌂ X	SEM	⌂ X	SEM
0-1	-10.90	1.20	-11.46	1.51
1-2	- 3.16	0.71	- 4.41	0.47
2-3	- 6.96	1.03	- 3.02*	0.60
3-4	- 0.02	1.16	+ 3.69**	0.81

(n=24)
* Different from Saline Treated-HAEG at $P<0.01$
** Different from Saline Treated-HAEG at $P<0.02$

DISCUSSION

Results presented here clearly demonstrate the high altitude effects in reducing body weight. Our data closely agree with those found by other authors in experiments of long-lasting discontinuous exposures (2, 8, 9) chronic exposure (10) and acute exposure (11) to simulated altitude. Cyproheptadine, 5-HT antagonist (12) prevented the dramatic body weight reduction during exposure to high altitude. Then, it is suggested that 5-HT is mediating the high altitude effects on body weight.

On the other hand, it has been shown that estradiol prevents the hypoxic effects on body weight (10) although through which mechanism, it had not been elucidated but for us, estradiol can be acting by means of 5-HT, since estradiol stimulates 5-HT transport in platelets (13) and there is substantial evidence that the platelets provide a suitable model for the reuptake of 5-HT into the presynaptic neurone (14). Recently, we had demonstrated a relationship between 5-HT and estradiol (15).

Stimulatory properties of estradiol over 5-HT uptake and anti 5-HT activity of cyproheptadine, would produce the same biological effects. In this study a minor reduction of body weight in high altitude exposure occurred when cyproheptadine was used and these results are similar to those obtained with estradiol treatment in male rats (10).

Further studies are indicated to determine whether cyproheptadine can be used in human beings when they are exposed to high altitude and if other effects observed when animals and human beings are exposed to altitude are dependent on 5-HT.

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