FINAL REPORT

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UNIVERSIDAD NACIONAL DE TRUJILLO
FACULTAD DE MEDICINA
APARTADO Nº 40
TRUJILLO - PERU - SUD-AMERICA

DEPARTAMENTO DE FISIOLOGIA

THE ROLE OF CATECHOLAMINES AND SEROTONIN IN THE PROCESS OF ADAPTATION TO HIGH ALTITUDE

Medina, A., Utano, L., and Olaya, G. Department of Physiology, Faculty of Medicine. Trujillo - Perú.

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INTRODUCTION

In the process of adaptation to high altitude, the circulatory and respiratory apparatuses do no act as isolated units. The hypoxia is an element which has a basic influence on them.

We have studied blood levels of Catecholamines and Serotonin in subjects at sea level and at high altitude (1). In this study we have found that the subjects at high altitude display a larger quantity of Serotonin in relation to those at sea level. On this basis, and knowing that the man who lives at a high altitude exhibits pulmonary hypertension (2, 3), we proposed to carry out a study of the role of Serotonin in pulmonary hypertension produced by hypoxia.

MATERIAL AND METHODS

Fifteen dogs with an average weight of 10.6 kg. were examined, only 7 of which we are presenting here. They were all anesthetized with Pentobarbital Sodium, at a dosage of 30 mg/kg of weight. A tracheotomy was carried out, a metal cannula being placed in each one, which was connected to a positive-pressure Harvard piston respirator which delivered the desired gas mixture at a constant stroke volume. The chest was opened through a thoracotomy in the fourth intercostal space left. The pressure in the left pulmonary artery was measured through a polyethylene catheter which was introduced from a segmental arterial branch (4). This catheter was

connected to Statham pressure transducer, and the pressure was recorded on a multichannel oscillograph of Grass.

For the purposes of the control, the dog breathed room air for 40 minutes and them was made breathe a mixture of 12.85% of 02 in N2 for 15 minutes, from a Douglas bag.

Blood samples were taken from the femoral artery for saturation of oxygen and pH, and blood from the pulmonary artery to determinate the Serotonin by Waalkes method (5).

These same dogs, after breathing the hypoxia mixture for 15 minutes, were made breathe room air for 20 minutes and then were injected with 20 ug/kg of weight of Methysergide+, waiting 30 minutes to make them breathe the hypoxia mixture.

RESULTS

Of the 15 experiments carried out, we are only taking the results of 9 in this report since the limitations in the use of Refrigerated Centrifuge meant that the Serotonin dosage could not be given to all.

The results of the mean pulmonary artery pressure are summarised in Table 1. We observe that with hypoxia a difference appears in relation to the control, of + 5.35 $\pm$ 1.4 mm Hg, this increase appearing more or less after 15 seconds and lasting the fifteen minutes of observation. When the dogs has been injected with Methysergide, the difference in the pressures is de -0.015 $\pm$ 0.7 mm Hg. This indicates to us that the hypoxia is producing an increase in the pulmonary artery pressure and that, on the antiserotonin being applied, the pressure does not increase.

The levels of Serotonin in pulmonary artery blood are expressed in Table 2. We can see that there is an increase of Serotonin during hypoxia, in relation to the control, of + 3.04 $\pm$ 0.13 ug/ml, taken after 15 minutes of hypoxia. When the animal is injected with Methysergide, there is a drop of -0.56 $\pm$ 0.04 ug/ml in relation to the control.

The saturation of hemoglobin by the 02 varied between 82-84% in hypoxia. The pH of blood was 7.3. In the animal injected with Methysergide with hypoxia the pH dropped to 7.04,

+ Deseril^{R} - Sandoz

resulting in death in more than 50% of the animals.

COMMENTARY

This study shows that hypoxia (breathing of 12.85% 02) produce an increase in pulmonary artery pressure. That this increase is due to an active vasoconstriction in the vascular pulmonary bed has been demostrated in dogs which have not been anesthetized as well as in those which have been anesthetized (6). Wilcox (4) suggests that this vasoconstriction is initiated by receptors in the systemic arterial system, presumably the aortic and carotid chemoreceptors, as has been established by Aviado (7).

We think that Serotonin must intervene as a chemical mediator in this reflex, since at the moment of hypertension an increase in it is produced in the pulmonary arterial blood. Moreover, by action of the antiserotonin no changes are produced in the pressure of the pulmonary artery in hypoxia or its response is less (8). With the action of Methysergide and hypoxia, the blood pH drops to 7.04, which results in the death of more than 50% of the animals. It is possible that this lack of Serotonin or blockage of the receptors causes the hypertension, which is necessary in hypoxia, not to be produced and an acidosis appears which causes the death of the animal. It is suggested that hypoxia produces a pulmonary hypertension of a reflex type, having Serotonin as a chemical intermediary.

SUMMARY

The effects of hypoxia (12.85% 02 in N2) on the pulmonary artery pressure of dogs have been studied, as well as the variations in the level of Serotonin in the blood of the same artery. Hypoxia produced pulmonary hypertension in the 7 dogs studied, and at the same time an increase in the level of Serotonin in the blood of the pulmonary artery was produced. This result is expounded in relation to a reflex vasoconstriction which is mediated by Serotonin.

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REFERENCES

1.- Medina, A., Utano, L., and Olaya, G. The role of Catecholamines and Serotonin in the process of adaptation to high altitude. Annual Report 1965-66, Grant AF-AFOSR-888-65. Presented in Symposium on Catecholamines. August 1966. Buenos Aires, Argentina, and VIII Congreso de la Asociación Latinoamerica de Ciencias Fisiológicas. Mexico, August 1967.

2.- Peñaloza, D., et al. Pulmonary Hypertension in Healthy men born and Living at High Altitudes. Am. J. Cardiol. 11: 150, Feb. 1963.

3.- Hultgren, H., et al. Pulmonary Circulation in acclimatized man at high altitude. J. Appl. Physiol. 20: 233, 1965.

4.- Wilcox, BR. et al. Effect of hypoxia on pulmonary artery pressure of dogs. Am. J. Physiol. 207: 1314, 1964.

5.- Waalkes, TP. The determination of Serotonin in Human Blood. J. Lab. Clin Med. 53: 824, 1959.

6.- Thilenius, OG., et al. Response of Pulmonary Circulation of resting, unanesthetized dogs to acute hypoxia. Am. J. Physiol. 206: 867, 1964.

7.- Aviado, DM., et al. Effects of Anoxia on Pulmonary Circulation: Reflex Pulmonary Vasoconstriction. Am. J. Physiol. 189: 253, 1957.

8.- Marco, V., et al. Acción de la Metisergide sobre las modificaciones producidas por la Serotonina en la circulación pulmonar del perro. Rev. Clin. Esp. 102: 29, 15 de julio, 1966.

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TABLE 1. Changes in pulmonary artery pressure with acute hypoxia

	Nº of dogs	Mean Pressure AP. mm Hg	Difference of Mean	P
CONTROL	7	23.21 ± 3.05		
HYPOXIA (12.85% 02)	7	28.56 ± 2.6	+ 5.35 ± 1.4	<0.01
METHYSERGIDE	7	19.15 ± 3.3		
METHYSERGIDE + HYPOXIA (12.85% 02)	7	19.70 ± 3.3	- 0.015 ± 0.7	>0.9

Values are reported as Mean ± SE

PA = Pulmonary Artery

TABLE 2. Levels of Serotonin in pulmonary artery blood with acute hypoxia.

	Nº of Dogs	Serotonin in PA blood. ug/ml.	Difference of Mean	P
CONTROL	7	0.700 ± 0.04		
HYPOXIA (12.85% 02)	7	3.55 ± 0.26	+3.04 ± 0.13	< 0.001
METHYSERGIDE + HYPOXIA (12.85% 02)	7	0.130 ± 0.15	-0.56 ± 0.04*	< 0.001

Values are reported as Mean ± SE

PA = Pulmonary Artery

* = Difference of Mean in relation to the Control