

Uptake of noradrenaline in high altitude native's heart

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Summary. Uptake of ^3H -noradrenaline by the heart was studied with sections of isolated atria obtained from high or lowlanders. In native highlanders, affinity for ^3H -noradrenaline by human atria is more significant than in lowlanders. Furthermore, the Michaelis Menten constant is lower in high altitude native's heart.

People born and residing permanently above 3500 m have a different circulatory pattern from lowlanders. Pulmonary hypertension and right ventricular hypertrophy were described previously¹. More recently, reduction in regional blood flow and in cardiac output were reported²⁻⁵. Decrease in local blood supply was accompanied by an increase oxygen arteriovenous difference in such a way that local oxygen consumption was maintained. However, there is an exception: reduction in coronary blood flow was not compensated by a parallel decrease of oxygen content in the blood of the coronary sinus, so that oxygen consumption related to heart weight was reduced in high altitude residents⁶.

These results may be related to changes in the noradrenergic nervous system. Studies carried out on rats artificially maintained in conditions of high altitude have demonstrated that the level of cardiac noradrenaline decreased during the period of acclimatization⁷⁻⁹ and subsequently returned to its normal rate, probably following decreased use of the transmitter. This was parallel to a slight decrease of the turn-over found in hypobaric hypoxia¹⁰, which may be due either to modifications of biosynthesis or to changes in the inactivation of nor-

adrenaline. This paper reports the differences in noradrenaline uptake main route of inactivation of the transmitter, studied on sections of human atria collected at high altitude or low altitude in Andean or European populations.

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Material and methods. 1.7-³H-noradrenaline (7.2 Ci/mmol) was obtained from the Radiochemical Center Amersham, England, 1-noradrenaline was from Calbiochem. Fragments of right atria were collected during surgery (congenital atrial septal defect) from persons of 20–50 years old, at low or at high altitude. The surgery was performed at high altitude (La Paz, Bolivia, 3,800 m) or at low altitude (Paris, 300 m). In both cases, these patients who had no history of congestive heart failure (i.e. myocardial catecholamines level does not change) were given the same medical treatment prior to surgery. Premedication included curarizing agents or morphine derivatives. After collection, the heart tissue was placed in cooled Mac Ilwain fluid. The 0.5 mm atria sections were obtained by means of a tissue slicer and incubated at 37°C in 3.5 ml oxygenated Mac Ilwain fluid in the presence of 1-³H-noradrenaline. Incubation was performed in the presence of 1 ng noradrenaline for 2, 5, 10, 15 and 20 min. In another series of tests, the sections were incubated for 10 min in the presence of increasing amounts of noradrenaline (10, 20, 50, 100 and 200 ng per ml of supernatant). After incubation, the sections

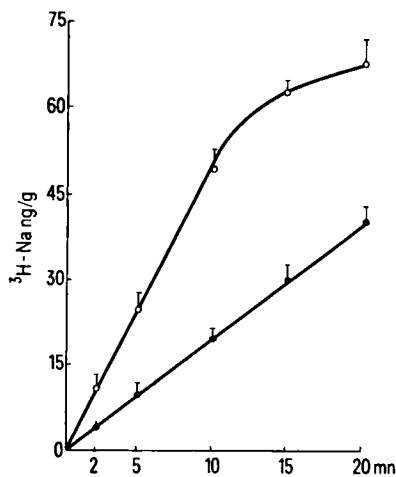


Fig. 1. Time-course of ³H-noradrenaline uptake in human atrium sections. The tissue was incubated in 10 ml of Mac Ilwain with 1 ng/ml of ³H-NA. ●—● lowlanders atria. ○—○ highlanders atria. Each point represents the mean \pm SEM from 5–7 determinations.

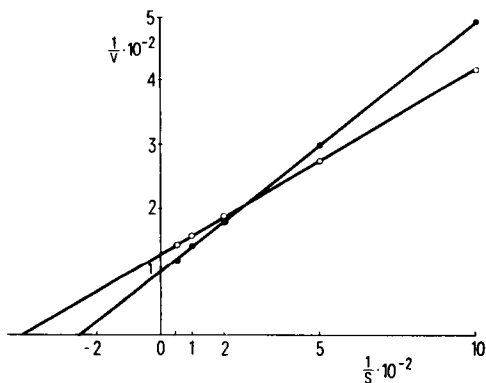


Fig. 2. ³H-noradrenaline uptake in atria from lowlanders or highlanders, plotted according to Lineweaver and Burk. The incubation time was 10 min. Each point is the mean of 5 determinations. The line was calculated by linear regression analysis, correlation coefficient = 0.96. Velocity (V) = uptake of ³H-noradrenaline ng/g 10 min. Substrate concentration S = ng/ml ³H-noradrenaline.

were rinsed with a cold buffer for a few seconds, dried on filter paper and weighed. They were then homogenized in 0.4 N perchloric acid containing 0.5% EDTA and 0.5% sodium metabisulfite. Noradrenaline was isolated by adsorption on alumina according to Anton and Sayre¹¹. Noradrenaline was eluted with 8 ml of 0.4 N HClO₄. An aliquot was taken for determination of ³H-noradrenaline by liquid scintillation counting. The rest was used for fluorimetric determination of noradrenaline¹². Recovery of noradrenaline was 79 \pm 3%.

Results and discussion. Figure 1 shows the kinetics of noradrenaline uptake by sections of human atria. Uptake of ³H-noradrenaline at a dose of 1 ng/ml was linear up to 20 min when the atrium fragment came from a low altitude resident. In native highlanders, affinity for ³H-noradrenaline was more significant than in lowlanders, but there was no linearity after 10 min. Noradrenaline level varied considerably depending on the patient's conditions and treatments. However, the average amounts observed of noradrenaline were 0.95 μ g/g \pm 0.15 in lowlanders and 1.20 \pm 0.20 in native highlanders. Although these variations were not statistically significant, they have an indicative value. Both in lowlanders and in native highlanders, noradrenaline uptake follows Michaelis-Menten kinetics (figure 2). The K_m and V_{max} were determined: (at low altitude, K_m = 0.23 μ moles and V_{max} = 100 ng/g min; at high altitude, K_m = 0.13 and V_{max} = 80).

The results showed that there are differences between affinities for noradrenaline uptake by atria from persons at high or low altitude. Using a 1 ng/ml dose of ³H-noradrenaline amine fixation takes place at neurone level and correlates with Iversen's uptake. Neuronal uptake was found to follow Michaelis-Menten kinetics, although the affinity is more significant for the uptake sites of the native highlanders. At low altitude, the values of K_m and V_{max} were of the same order of magnitude as those found in rats using a perfusion technique of the isolated heart according to Iversen et al.¹³, and those found in man after incubation of tissue sections¹⁴. In spite of the in vitro conditions, the endogenous noradrenaline content of the atria was close to the one previously reported^{15, 16}. The quantitative difference observed between noradrenaline uptake in lowlanders and highlanders is related to the more significant affinity found at high altitude. This result may be due to a more efficient uptake of noradrenaline by the axon membrane pump, which reduces catecholamine wastage and secondarily induces the slight increase of endogenous noradrenaline. This action should be parallel to the decreased oxygen demand of the heart cells, and the decrease of noradrenaline turn-over rate. However, one may ask what is the triggering factor: is it the function of the membranous pump for noradrenaline, the decrease of the noradrenaline turn-over rate, or the decrease of oxygen consumption?

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