Histamine – an important Mediator for the Euler-Liljestrand Mechanism?*

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Abstract. During normoxia and acute alveolar hypoxia the pulmonary vascular-resistance, histamine concentrations in the lung parenchyma and partially in the arterial blood, and cAMP levels in the lung tissue of young pigs were measured. A significant correlation between the pulmonary vascular resistance and the lung or blood histamine concentrations was not found during either normoxia or hypoxia. The influence of terbutaline and meclastine on the pulmonary vascular resistance and biochemical parameters was also studied. Terbutaline significantly reduced the hypoxic pulmonary vascular response. An inverse relation between the pulmonary vascular resistance and the cAMP levels during the drug induced inhibition of the Euler-Liljestrand mechanism was found. Meclastine had no influence on the hypoxic pressor response.

Keywords: Pulmonary circulation-Euler-Liljestrand - Hypoxia - Histamine - cAMP - Terbutaline - Meclastine.

Histamine has been know as one of the most powerful pulmonary vasoconstrictors since the experiments of Dale [3]. More and more investigations of the role of vasoactive substances as mediators of the pulmonary vasoconstrictor response to acute alveolar hypoxia suggested that endogenous histamine was important for this mechanism. Hauge and Melmon demonstrated the inhibition of the Euler-Liljestrand mechanism in isolated rat and cat lung preparations induced by the histamine depleting compound 48/80. Antihistamines of various pharmacological groups were effective in reducing the hypoxic vascular response when administered before the onset of acute hypoxia [7, 8]. Similar results were obtained by Susmano and Carleton, who found a reduced elevation of the pulmonary vascular resistance (pVR) in intact dogs when chlorpheniramine or promethazine were injected either before or during exposure to hypoxia [22, 23].

The importance of the periarterial mast cells as a storage depot of a locally effective mediator was extensively discussed by Haas and

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Bergofsky [6], who showed lung mast cell degranulation and histamine release of peritoneal mast cells during acute hypoxia.

Additional observations [6] correlated the increment in pvR during hypoxia and the amount of radioactive-labeled histidine converted to histamine and released by the lung; these findings confirmed previous results of Aviado [1].

Morphological studies in chronically hypoxic rats documented hyperplasia of the lung mast and a significant increase of the mast cell number [16]; the histamine forming capacity, however, seems to remain unaffected [10]. The discrepancy between the action of exogenous histamine on the pvR in isolated lungs resulting in a marked pvR increase and the action of histamine on the intact animal was solved by Colebatch, who suggested that epinephrine was released from the adrenal glands following histamine administration. Surgical as well as pharmacological adrenalectomy uncovered a prolonged increase of the pvR that was absent in non-adrenalectomized animals [2].

Previous results of Sill et al. [21, 9, 20, 25] provide some evidence for the mediator role of the adenylcyclase-cAMP-calcium system for the alveolar-vascular reaction. In the present time-course study we have tried to approach the mediator problem by comparing the effects of a β-sympathicomimetic drug and an antihistamine on the pvR and the lung histamine and cAMP levels during acute hypoxia.

METHODS

Twelve young pigs with an average weight of 21 kg were used for the experiments; the animals were anesthetized by an i.p. injection of pentobarbital sodium (Nembutal®) (30 mg/kg) which was followed by a maximum dose of 16 mg/kg pentobarbital during the experiment. Intermittent positive pressure breathing with a oxygen-N2O mixture was administered. The respiratory pressures remained constant during the experiment; hypoxia was controlled by the reduction of the oxygen content of the breathing mixture only.

A thoracotomy was performed, plastic microcatheters were placed in the pulmonary artery, the femoral artery and vein and the left ventricle was punctured from the apex with a steel cannula (inner diameter 1.4 mm). Pulmonary artery pressure (PAP), the left ventricular pressure (LVPs), femoral artery pressure (AoPm), and central venous pressure were measured with strain gauge pressure transducers (Statham 23 Dbl). The contractility parameter dp/dtmax was obtained by an electronic differentiator (Hellige, Germany). The left ventricular end diastolic pressure was estimated from the pressure curves recorded on a Siemens Mingograph. The cardiac output (HMV) was measured with an electromagnetic flowmeter (Hellige SQ 401); the flowmeter probe (Statham-Flo-Probe, inner diameter 12 mm) was fixed to the pulmonary artery approximately 2 cm distally from the pulmonary valve. The hemodynamic data were recorded at 3 min intervals. 21 min after the onset of hypoxia 0.01 mg/kg terbutaline (Bricanyl®) and 42 min after the onset of hypoxia 0.56 mg/of meclastine (Tavegil®) were injected via the pulmonary catheter over a 3 min period.