LUNG AS A METABOLIC ORGAN

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Because of lungs special position in the circulatory system, the pulmonary circulation has, in addition to its role in the exchange of gases, an important role in homeostasis. Metabolic activities of the lung include exogenous and endogenous functions. Through the endogenous metabolic functions, pulmonary circulation provides energy and maintains homeostasis of lung cells. Through the exogenous metabolic functions, pulmonary circulation modulates the homeostatic mechanism of the entire body. The extracting of hormonal and excitatory substances during pulmonary circulation is, collectively, referred to, as metabolic activities of the lungs.

To consider the lung as an important metabolic organ with active functions, other than those associated with gas exchange, is a relatively new concept.[1-8] In 1925, Starling and Verney[9] found that they could not maintain adequate circulation through an isolated perfused kidney with a simple perfusion circuit. They removed this substance by perfusing the kidney from a heart-lung preparation and concluded that the blood was detoxicated in the lungs. The isolation of serum vasoconstrictor substance and its identification as 5 HT by Gaddum[10] started a whole new avenue of research. The hepatorenal syndrome is believed to be caused by the failure of the lungs to remove the biogenic amines such as 5 HT[11] However, the published information on the metabolic activities of lung tissue is sparse when compared with relating to the respiratory function of lungs in both health and disease.

The lung is a complex organ with about 40 different constituents cell types.[12] Epithelium lining of the air spaces, and the endothelium,, which receives the cardiac output are by far the most investigated cell types in the lung. Pulmonary endothelial cells are the most likely to be responsible for many metabolic functions as a result of their continuous and direct access to the total cardiac out put. Because of their strategic position, number and functional capability, lung endothelial cells control the composition of arterial blood.

Ryan et al[13] have shown that the an giotensin-converting enzyme is linked with the endothelial cell membrane and vesicles opening to the blood front. Ryan et al[14] also demonstrated that bradykinin inactivated by an enzyme located on the luminal surface of endothelial cells. In short, lung endothelial celis monitors the regulation of substances such as bradykinin, which is responsible for lowering the blood pressure and on the other hand, angiotensin II which raises blood pressure. Nonetheless, both the substances enter the arterial circulation.

The methods available to study lung metabolic activities can be divided into three main groups:

1. Invivo methods
2. Invitro methods
3. Perfused lung preparations

Invivo methods elicit an overall diagram of arterio-venous differences across the organ. Invitro methods include the use of either tissue slices, homogenates, minces, isolated cells, sub-cellular fractions, or cells in cultures. Invitro and perfused lung preparations have yielded important results and insights, however, they are limited by the fact that either cell tissue or organ environment is disturbed in such a way as to introduce experimental artifacts. Monoamines metabolism has been studied in the lung homogenates,, lung slices and perfused lung isolation[15] The enzymatic properties are, however, not reliable index to the enzymatic properties of the lung invivo. Enzymes and membranes from intracellular origin contaminate the cellular membrane in homogenates and slices. Competition of the liver vascular bed and all other body vascular beds for ligands are excluded in perfused lung preparations. Effros[16] suggested imaging of tracers to overcome these limitations.

The first noninvasive technique to study metabolic activities of the lung based on dual indicator dilution technique using nuclear medicine imaging methodology was developed by Syrota et al[17]. This technique is essentially a noninvasive modification of Chinard-Crone's technique. Similarly, Akber[18] and Rahimian et al[19] used N-Isop ropyl-l23-p- lodoamphetamine (IMP) in dogs to monitor the physiological aspect of amine metabolism.

Metabolic process primarily determines the functions of microvasculator endothelial cells of the lung. But if endothelial damage is a frequent response of lung injury, it seems probable to anticipate simultaneous changes in one or more of the metabolic functions of these cells. Block and Fisher[20] reported that endotheliumdestroying hyperoxia is linked with a decrease in 5 HT clearance. This is of particular clinical importance since the pulmonary endothelial cell is known to be the primary site of damage in a number of disease states, including oxygen toxicity, adult respiratory distress syndrome (ARDS), radiation pneumonities, and a variety in ARDS, characterized by pronounced changes in lung mechanics, oxygenation, and perfusion. It is estimated that ARDS effects 150,000 patients every year in the USA[21]. Sadly, despite intensive clinical and laboratory investigations, the human ARDS survival rate since 1967 is virtually unchanged.[22]

Syrota et al[17] have shown that patients with chronic obstruction of pulmonary disease (COPD) have significant decrease in the pulmonary extraction of C-il chlorpromazine (CPZ). The data of Gillis et al[23] suggest that observed reduction in pulmonary amine removal probably reflect direct endothelial damage rather than a change in the volume of lung vasculature perfused. Akber[18] and Akber et a1[24] have used ketamine and propranolol to simulate the destruction in the pulmonary endothelial as well. It has been found that the fIrst pass pulmonary extraction of IMP is reduced as the dose of interventional drug increases. This study simulates Syrota et a1[17] work. With COPD the first pass extraction of C-i 1 CPZ measured was 64% while IMP extraction measured were 64% and 62% respectively for dosage of 100 mg of ketamine and 10 mg of propranolol. Furthermore, it has recently been shown by Touya et a1[25] that radioimmunoassay principle could also be applied to assess pulmonary endothelium.

Invivo examination of metabolic extraction provide basic information on amine uptake and metabolism useful in clinical studies of both normal and pathologic states. The importance of this technique can be seen not only in dynamic studies of labeled compound uptake but also in various pharmacological and pathological conditions influencing drug metabolism. This technique might have considerable application in clinical studies in nuclear medicine, where a relatively simple and safe noninvasive determination of metabolic process might provide additional diagnostic information.

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