THE PULMONARY DISPOSITION AND METABOLISM OF 5-HYDROXYTRYPTAMINE

by

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SUMMARY

The role of serotonin (5HT) in the functioning of the mammalian organism has been a matter of considerable speculation since its identification some 25 years ago. The presence of high quantities of this vasoactive amine in the lung has not escaped notice. Suggestions as to the possible role of 5HT in processes such as pulmonary vascular hypertension, pulmonary embolism, anaphylaxis and control of ventilation perfusion balance have been made but not established. This thesis is an effort to elucidate some of the basic interactions between 5HT and the lung especially in regard to its uptake and storage in the intact animal.

Tracer doses of ^{3}H-5HT administered i.v. to mice and rats are rapidly accumulated in the lung with subsequent long term retention of the unchanged amine. In mouse lung, levels of ^{3}H-5HT appear to follow a first order monophasic decya with a $t_{1/2}$ of greater than 100 hours. Further studies indicate that there is no differential between the levels of ^{3}H-5HT in platelet "rich" and platelet "poor" plasma, although there is a 7.5 to 1 ratio of the number of platelets in the two fractions. The half-life of 5HT in the lungs is considerably longer than the reported half-life of 5HT in the platelet. Thus, it appears that the uptake and retention of administered ^{3}H-5HT is not entirely a function of the retention of labelled amine by platelets in the lung. Imipramine and reserpine increase the efflux of ^{3}H-5HT from the lungs. Since reserpine reportedly has no effect on the 5HT content of mast cells, the drastic reduction in ^{3}H-5HT levels in the lung suggest that the mast cell is not responsible for the

uptake and retention of labelled amine. The benzo[b]thiophene analog of 5HT produced no decrease in the lung levels of ^{3}H-5HT thus alluding to the structural specificity of the uptake and/or storage mechanisms. The adrenergic neuron blocking drug, guanethidine also has no effect on the levels of ^{3}H-5HT found in the lung. Previous reports indicate that this drug reduces 5HT levels in the brain but not the intestine. The nature of the lung storage of the amine, then, appears to resemble that of the intestine.

Thin layer chromatography of methanol/acetone extracts of lungs from mice sacrificed at time points ranging from 15 min to one week after ^{3}H-5HT injection reveal the presence of only one minor metabolite. Bidimensional thin layer chromatography of lung extracts to which ^{14}C-5HIAA was added showed this metabolite to be 5HIAA.