Title : EFFECT OF HALOTHANE ON UPTAKE AND METABOLISM OF 5-HYDROXYTRYPTAMINE BY RAT LUNGS PERFUSED IN SITU

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Introduction. Pulmonary endothelium is an important site of metabolism of circulating vasoactive substances. Endothelial cell function may be modified upon exposure of lungs to anesthetic agents, hypoxia or other compounds which alter cellular metabolism. Thus, the effects of halothane on uptake and metabolism of circulating 5-hydroxytryptamine (5-HT) by perfused rat lungs was investigated.

Methods. Lungs were perfused in situ for 60 min. (1) with recirculating Krebs-Henseleit bicarbonate buffer containing 4.5% bovine serum albumin, 5 mM glucose, normal plasma levels of 19 amino acids and 690 μM [^{3}H]phenylalanine. Buffers were equilibrated and lungs ventilated (tidal volume, 1.0 ml/100 g body wt.) with humidified 20% O_2: 75% N_2: 5% CO_2 ± 4% halothane. Uptake and metabolism of [^{14}C]5-HT was estimated during a subsequent 2 min. period of flow-through perfusion. Perfusion pressure was held constant at 20 cmH_2O. Tissue and perfusate 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) were estimated by ion-exchange chromatography (2). Protein synthesis and lung ATP were measured as described earlier (1,3).

Results. Uptake of [^{14}C]5-HT (specific activity 2 x 10^3 dpm/nmol) by perfused rat lungs was linear for at least 2 min. and was unaffected by iproniazid (IP, 0.5 mM); IP inhibited conversion of 5-HT to 5-HIAA by 92%. Imipramine (20 μM) reduced uptake and metabolism of 5-HT by 60%. Metabolism of 5-HT to 5-HIAA exhibited saturation kinetics with an apparent K_m and V_{max} of 2.03 μM and 7.1 nmol/g·min., respectively. At 20, but not at 2 μM perfusate 5-HT, halothane exposure (60 min.) increased lung 5-HT 65%. Halothane did not affect 5-HIAA or 5-HT + 5-HIAA (Fig. 1). In the presence of halothane, pulmonary flow (19 ± 1 ml/100 g body wt.·min.) and sorbitol space (0.29 ± .01 ml/g) were unaltered; lung ATP remained constant. Synthesis of lung proteins was reduced 24% ($p < .05$) by halothane (Table I).

Discussion. Halothane altered metabolism of 5-HT at high but not at low substrate levels. Accumulation of 5-HT in the presence of halothane could reflect inhibition of 5-HT metabolism or altered distribution of the vasoactive amine. Direct measurements, however, indicated that vascular resistance and extracellular space were unchanged by the anesthetic gas. Thus, these observations are consistent with reduced capacity of the lung to metabolize 5-HT in the presence of halothane. In addition, halothane inhibited synthesis of lung proteins. Inhibition of 5-HT and protein metabolism without ATP depletion suggested that halothane may act selectively in lung tissue. Further studies are required to determine the specificity of these changes, as well to define their reversibility.

Parameters	Control	Halothane
Lung ATP, μmol/g dry	8.9 ± 0.3(6)	8.5 ± 0.4(10)
Phenylalanine Incorporation, 10^{-3}·dpm/mg protein·hr	3.8 ± 0.3(8)	2.9 ± 0.2(12)*

*$p < .05$

Table I. Effect of halothane on lung ATP and phenylalanine incorporation.

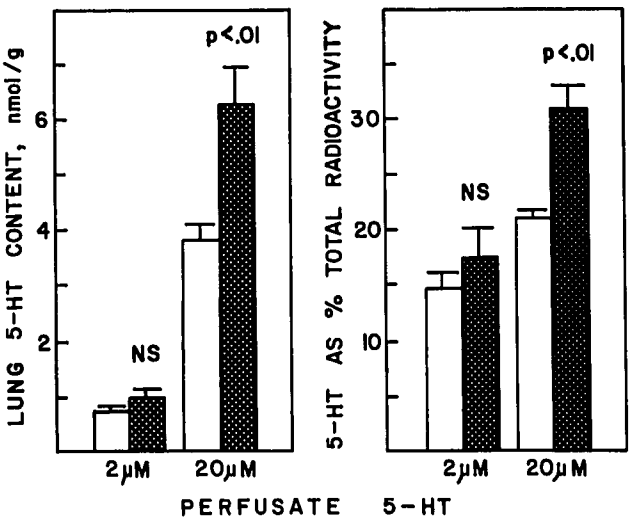

Figure 1. The effect of halothane exposure (shaded bars) on lung 5-HT content is shown in the left panel. The fraction of total lung radioactivity present as 5-HT is shown in the right panel. Measurements were made after a 2 min. exposure to [^{14}C]5-HT. Data represent the mean ± S.E.M. of 6 to 10 observations.

References.

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