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Accumulation and metabolism of [^{14}C]histamine by rat lung *in vivo*

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The ability of the mammalian lung to provide a metabolic as well as a ventilatory function has been established over the past decade [1–4]. Included among those substances which can be accumulated and/or metabolized by this organ are the following: norepinephrine [5–7], epinephrine [5], isoproterenol [8], 5-hydroxytryptamine [6, 9, 10], bradykinin [11] and prostaglandins of the E and F series [12]. While rat lung inactivates norepinephrine [5, 7], epinephrine [5] and 5-hydroxytryptamine [9, 10], it has been suggested that this tissue does not remove histamine from the circulation [13, 14]. Since chopped lung from this species has been shown to metabolize this amine [15], the ability *in vivo* of rat lung to accumulate and/or degrade exogenous histamine has been re-examined using a sensitive radiometric technique.

Adult male Sprague–Dawley rats (Charles River) weighing 150–250 g were injected i.v. with 1 μCi/200 g of [ring 2-^{14}C]histamine (sp. act. 57–59 mCi/m-mole, Amersham/Searle Corp., Arlington Heights, IL). At varying time intervals after injection, the animals were decapitated; the lungs were removed or the blood was collected in a heparinized centrifuge tube and the plasma prepared. After resection, the lungs were perfused through the pulmonary artery with ice-cold 0.9% NaCl, minced with scissors and homogenized in 10 vols of 0.4 N $HClO_4$. After standing for 15 min in the cold (4°), the homogenate was centrifuged at 1000 *g* for 15 min. A 100-μl aliquot of the resultant supernatant was counted in a liquid scintillation spectrometer (Packard Instrument Co.) for determination of total ^{14}C. The remainder of the supernatant was extracted according to the technique of Snyder *et al.* [16] for determination of [^{14}C]histamine. Plasma was mixed with an equal volume of 0.8 N $HClO_4$, allowed to stand for 15 min, centrifuged at 1000 *g* for 15 min and then treated in a manner identical

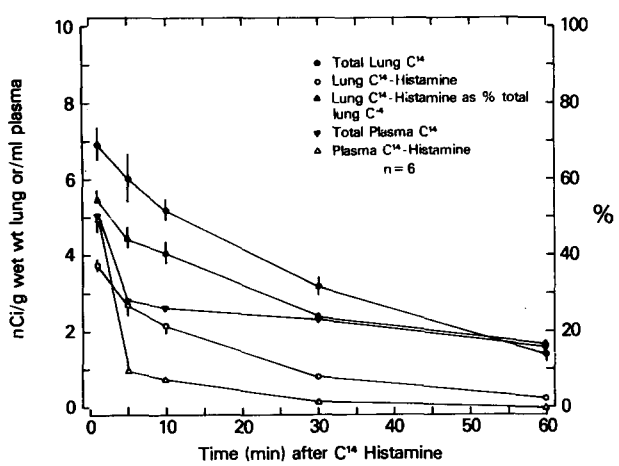

Fig. 1. Time course of lung and plasma levels of total ^{14}C and [^{14}C]histamine after the i.v. administration of 1 μCi/200 g of [^{14}C]histamine to rats; n = number of animals. Values are mean ± S.E.M. Where the S.E.M. is omitted, it was smaller than the symbol for the mean.

Table 1. Effect of aminoguanidine and iproniazid on the accumulation and metabolism of [^{14}C]histamine by rat lung*

Compound	Dose (mg/kg)	N†	Total lung ^{14}C (nCi/g)	P‡	Lung [^{14}C] histamine (nCi/g)	P‡
Saline		6	6.30 ± 0.47		2.46 ± 0.24	
Aminoguanidine	25.0	6	6.50 ± 0.55	>0.05	6.20 ± 0.48	<0.05
Iproniazid	100.0	6	5.66 ± 0.28	>0.05	5.72 ± 0.31	<0.05

* Rats were treated with the compounds i.p. 60 min prior to the i.v. administration of 1 μCi/200 g of [^{14}C]histamine and killed 10 min later.
† Number of animals.
‡ Significance cf. saline.

to that described above for lung. [^{14}C]histamine was corrected for a recovery of 68 per cent. Results were analyzed using Student's '*t*' test.

Figure 1 illustrates total ^{14}C in lung and plasma at time intervals ranging from 1 to 60 min after administration of [^{14}C]histamine. At all time periods up to 60 min, lung-^{14}C exceeded plasma-^{14}C by factors ranging from 1.4 to 2.10, after which tissue/plasma levels were about unity. Similarly (Fig. 1), lung [^{14}C]histamine levels exceeded those of plasma at the 5-, 10- and 30-min times by factors ranging from 1.5 to 5.0. The percent of total lung-^{14}C represented by unchanged [^{14}C]histamine declined from an initial high of 55 at 1 min to 16 at 60 min. These data demonstrate a removal and subsequent metabolism of [^{14}C]histamine from the circulation by rat lung. Moreover, the results suggest that tissue accumulation and metabolism of [^{14}C]histamine exceed the rate at which metabolites are lost. The apparent slow loss of metabolites may be accounted for by one or both of the following: (1), the less favorable tissue to plasma-^{14}C gradient seen at longer time periods; or (2) a possible accumulation of circulating metabolites by the tissue. It is not possible, at present, to discriminate between these possibilities.

Table 1 highlights the effect of aminoguanidine and iproniazid, inhibitors of histaminase [17], on the accumulation and metabolism of [^{14}C]histamine. After administration of these compounds, virtually all lung-^{14}C was accounted for as [^{14}C]histamine, suggesting that oxidative deamination is the major metabolic pathway in rat lung, as suggested by others [15]. When animals were treated i.p. 60 min prior to [^{14}C]histamine and killed 10 min after, the following compounds had no effect on lung accumulation or metabolism: chlorpromazine, 5 mg/kg; phenoxybenzamine, 5 mg/kg; propranolol, 5 mg/kg; mepyramine, 5 mg/kg; disodium cromoglycate, 5 mg/kg; and amodiaquin, 100 mg/kg. Similarly, reserpine (5 mg/kg, 20–24 hr prior to [^{14}C]histamine administration) failed to alter either accumulation or metabolism.

Thus, under the present experimental conditions, rat lung appears capable of accumulating and metabolizing circulating histamine. The experimental design *in vivo* employed in this study departs considerably from the isolated perfused lung system used to document the accumulation and metabolism of other amines by rat lung. Consequently, additional studies are necessary to evaluate the extent of similarities and/or differences in the uptake processes for the various amine substrates.

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