Metabolism *in vivo* and *in vitro* of radiolabelled histamine and *tele*methylhistamine in rat brain

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The putative central neurotransmitter histamine is metabolised mainly, if not solely, by methylation in the brain of the rat and other species (see review by Schwartz, 1977). The product *tele*methylhistamine is metabolised further to *tele*methylimidazoleacetic acid (nomenclature of Black & Ganellin, 1974). Waldmeier, Feldtrauer & Maître (1977) have shown that this deamination is catalysed by monoamine oxidase B. A number of groups have studied the *in vivo* and *in vitro* metabolism of [^{14}C]-histamine in the brain. Rothschild & Schayer (1958) studied the peripheral metabolism of [^{14}C]-methylhistamine in mice; however, we are not aware of any study of the metabolism of [^{14}C]-methylhistamine in brain.

[^{14}C]-Histamine (295 mCi/mmol) was obtained from the Radiochemical Centre, and [^{14}C]-*tele*methylhistamine (295 mCi/mmol) was prepared from [^{14}C]-histamine by enzymatic methylation (Knight, Morecombe, Saunders & Smith, in preparation). The procedure used for *in vivo* and *in vitro* metabolism, and for separation and quantification of radiolabelled metabolites, is described elsewhere (R.I. Knight & I.R. Smith, submitted as Demonstration to this meeting).

[^{14}C]-Histamine (200 ng, 44300 d/min) administered into the right lateral ventricle was rapidly metabolised to [^{14}C]-methylhistamine and [^{14}C]-methylimidazoleacetic acid, as previously reported (see review by Schwartz, 1977). Only a small amount (approx. 200 d/min) of the [^{14}C]-histamine remained after two hours. [^{14}C]-Methylhistamine (200 ng, 41000 d/min) administered intracerebroventricularly was metabolised as expected by oxidation into [^{14}C]-methylimidazoleacetic acid. There was a fall in [^{14}C]-methylhistamine levels over a 2 h time period, with a concomitant rise in [^{14}C]-methylimidazoleacetic acid. Only a small amount (approx. 1200 d/min) of the [^{14}C]-methylhistamine remained after two hours.

In vitro metabolism of [^{14}C]-methylhistamine has also been investigated. Incubations were carried out in duplicate, with good agreement between duplicates. A homogenate of whole brain in 5 ml of phosphate buffer (0.1 M, pH 7.4) was incubated for 1 h with [^{14}C]-methylhistamine (10 μM), resulting in [^{14}C]-methylhistamine and [^{14}C]-methylimidazoleacetic acid in the ratio 95:5. A similar experiment, in which the brain was homogenised in 12 ml of Krebs bicarbonate buffer and incubated for 1 h with [^{14}C]-methylhistamine (2.5 μM) under 95% O_2:5% CO_2 gave substantially greater oxidation, the ratio of [^{14}C]-methylhistamine to [^{14}C]-methylimidazoleacetic acid being 58:42.

Another aspect of the metabolism of [^{14}C]-methylhistamine in which we were particularly interested was the possibility that this substance might be demethylated, yielding [^{14}C]-histamine. The chemical analogy for such a process would be that N-substituted acyl- and silylimidazoles are used as acylating and silylating agents respectively. The rapid *in vivo* methylation of [^{14}C]-histamine observed might preclude the detection of any [^{14}C]-histamine formed from [^{14}C]-methylhistamine in an *in vivo* experiment. We therefore investigated this aspect further in *in vitro* experiments. Under conditions where it was established that any [^{14}C]-histamine generated would not be substantially remethylated (by including unlabelled histamine (10 μM) in the incubation medium), we were unable to detect any (i.e. > 0.5%) [^{14}C]-histamine formed from [^{14}C]-methylhistamine.

References

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