When freshly isolated, mitochondria from chlorpromazine-treated animals oxidized succinate at rates similar to those of the controls. However, mitochondria from the treated guinea-pigs and rats showed some loosening of respiratory control with glutamate and pyruvate, substrates linked to nicotinamide adenine dinucleotide (NAD^+). An increase in the basal (state 4) rate of mitochondrial respiration was accompanied by a corresponding decrease in RCI. Rates of oxidation of the same substrates by cat heart mitochondria were unaffected by chlorpromazine treatment. In all three species, ADP:oxygen ratios remained unchanged.

Storage of isolated mitochondria results in loss of respiratory control (Slater & Hülsmann, 1959); oxidative phosphorylation is subsequently uncoupled; and finally respiratory activity fails. In the present experiments, mitochondria isolated from the control animals showed this characteristic loss of respiratory control when kept for 4 hr at 0°C. In contrast, respiratory control of the stored mitochondria isolated from chlorpromazine-treated animals was maintained or even increased and basal rates of NAD^+-linked substrate oxidation reduced.

The chlorpromazine-induced changes which were observed with freshly isolated mitochondria suggest an effect of the drug on the first phosphorylation complex of the electron transport chain, while the experiments with stored mitochondria indicate a stabilization of the mitochondrial membrane.

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Evidence that 1-methylimidazole-5-acetic acid is not a metabolite of histamine.

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The major metabolite of histamine in man is 1-methylimidazole-4-acetic acid (1-MeIm4-AA). Both this compound and its isomer 1-MeIm5-AA are normally present in human urine (Tham, 1966a; Granerus, 1968). The origin of the 1,5-isomer is uncertain, but it is probably not a histamine metabolite (Tham, 1966b). Although small doses of histamine are not metabolized to 1-MeIm5-AA in mammals (Schayer, 1959), mice metabolize large doses of histamine to both 1-MeIm4-AA and 1-MeIm-5-AA (Karjala & Turnquest, 1955). We have measured these compounds in urine by gas chromatography (Kelvin, 1970). Our results indicate that 1-MeIm5-AA is not a catabolite of histamine.

The 24 hr excretions of 1-MeIm4-AA and 1-MeIm5-AA by a healthy adult male volunteer were 2·99 mg and 1·92 mg respectively. After histamine (8 mg/kg orally), which resulted in moderately severe hypotension, flushing and headache, the values were 56·9 mg and 2·04 mg. Thus in this man histamine was not metabolized to 1-MeIm5-AA.

The urine of male Swiss albino mice injected with [^{14}C]-histamine (7 μg/kg) was analysed for [^{14}C]-methylimidazoleacetic acids by gas chromatography, radioactive peaks being located as described by Robbins & Bakke (1967). Approximately 40% of the radioactivity was found in the peak corresponding to 1-MeIm4-AA, but none corresponding to 1-MeIm5-AA, thus confirming Schayer's results.

The mean 24 hr excretion of histamine and 1-MeIm4-AA in male mice during a control period of subcutaneous saline injections was 3 μg and 16 μg respectively. There was no excretion of 1-MeIm5-AA. During daily treatment with histamine (250 mg/kg subcutaneously) for 4 days the corresponding values were 3,000 μg and 213 μg respectively, but there was still no excretion of 1-MeIm5-AA. These results, therefore, do not confirm Karjala & Turnquest's (1955) findings.

Further evidence that 1-MeIm5-AA is not a histamine catabolite was obtained during some studies on the effect of enzyme inhibitors on histamine metabolism. Under standardized dietary conditions (Granerus, 1968) a healthy adult male volunteer excreted $3{\cdot}52 \pm 0{\cdot}07$ mg 1-MeIm4-AA and $1{\cdot}91 \pm 0{\cdot}12$ mg 1-MeIm5-AA per 24 hr (mean $\pm$ S.E. of mean, $N=5$). Treatment with tranylcypromine (10 mg orally every 8 hr) reduced the 24 hr excretion of 1-MeIm4-AA ($2{\cdot}68 \pm 0{\cdot}13$ mg, $N=3$, $P<0{\cdot}001$) but not that of the 1,5-isomer ($2{\cdot}33 \pm 0{\cdot}24$ mg). These results support the view that methylhistamine is oxidized to 1-MeIm4-AA by monoamine oxidase *in vivo*, because tranylcypromine is believed to be a relatively specific inhibitor of this enzyme, and also clearly indicate that the 1-MeIm4-AA and 1-MeIm5-AA arise through different biochemical pathways. It is therefore improbable that the 1-MeIm5-AA which occurs in human urine is a metabolite of histamine formed by oxidation of 1-methyl-5-(2-aminoethyl) imidazole.

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A model noradrenaline binding site.

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Immunoglobulins specific to noradrenaline have been prepared in rabbits by injection of a noradrenaline-bovine serum albumin complex. The immunoglobulins were extracted from the antisera by adsorption on to an insoluble polymer of the immunizing antigen with subsequent desorption by a related hapten. Complex formation between the immunoglobulin and various haptens structurally related to noradrenaline have been studied by a fluorescence quenching method. Association constants of the order of 10^6 to 10^7 l. mol^{-1} were obtained for the reaction : Hapten + immunoglobulin (IgC) $\rightleftharpoons$ IgC-hapten.