Inhibition of Histamine Formation *in vivo*

Quantitative studies of the inhibition of histidine decarboxylase *in vivo* are now feasible with the introduction of two methods of assessing the rate of endogenous histamine formation in the rat. One method, devised by Schayer, measures the amount of ^{14}C-histamine excreted in the urine following the injection of a known amount of ^{14}C-histidine. The other method depends on the demonstration that in the female rat the urinary excretion of free histamine parallels the endogenous formation of the amine[1,2]. Using both these methods, it was found that omitting pyridoxine from the diet for a week causes a reduction in histamine formation to about half normal, and that the rate of formation can be reduced further by superimposing injections of semicarbazide on the pyridoxine-deficient diet[3].

In the present work α-methyl-histidine was found to be a more specific and less toxic inhibitor of histamine formation than semicarbazide, which is known to inhibit a variety of enzymes, among them various amino-acid decarboxylases and diamine oxidases. α-Methyl-histidine was provided by Merck, Rahway, New Jersey, through the kind office of Dr. Schayer. This compound was tested in two types of experiments. One group of rats was fed the standard, adequate, histamine-free diet[1]. In another group pyridoxine was omitted from the diet until a reduced steady level of histamine formation was obtained, and α-methyl-histidine administered while the deficient diet was maintained. This was done to see whether inhibition of histamine formation by this compound was due to interference with the active centre of histidine decarboxylase or merely to an action on the co-enzyme pyridoxal-5-phosphate, the probable mode of action of semicarbazide. In addition, the urinary excretion of 5-hydroxyindolyl acetic acid (5-HIAA), which is believed to reflect the rate of endogenous formation of 5-hydroxytryptamine (5-HT), was followed. This, again, was carried out to see if α-methyl-histidine also inhibits the formation of 5-HT, which is known to result from hydroxylation of tryptophan to 5-hydroxytryptophan and the subsequent decarboxylation of this amino-acid.

Typical results in a rat fed the adequate diet are shown in Fig. 1; α-methyl-histidine injected under the skin in doses of 200 mgm./kgm., 4 times daily during four days, results in a reduction of the over-all formation of histamine, as determined by the urinary excretion, to less than half normal. On discontinuing the injections the original level of histamine formation is promptly restored and even transitory rebounds above this level are seen. The excretion of 5-HIAA, by contrast, remains unaltered.

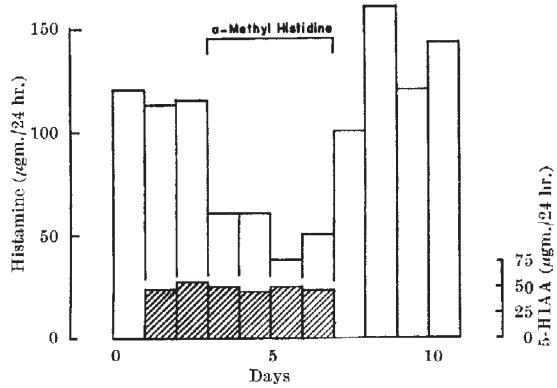

Fig. 1. The white columns represent amounts of daily excretion of free histamine in a female rat fed an adequate histamine-free diet. The hatched columns represent daily urinary excretion of 5-HIAA. α-Methyl-histidine was injected for a period of four days. Aminoguanidine was administered during the entire course of observations to prevent the inactivation of histamine by histaminase

In the group of rats on deficient diet, in a typical example, deficiency in pyridoxine for 24 days reduced the level of urinary histamine to about 40 per cent of normal, whence it remained steady for the period of observation. Superimposing injections of α-methyl-histidine on the maintained deficient diet, 4 × 200 mgm./kgm. daily for 4 days, beginning at the 24th day of deficiency, precipitated a further reduction in the formation of histamine to about half the level prevailing after 24 days of only pyridoxine deficiency. On cessation of the injections the level of urinary histamine promptly rose to the level at which administration of the inhibitor was begun. In the same group of rats ^{14}C-histidine was injected and the urinary ^{14}C-histamine measured, first on adequate diet, then at the reduced steady level of pyridoxine deficiency, and finally under conditions of superimposed injections of α-methyl-histidine on the deficient diet. The results with the radioactive method were the same as with the simpler one used simultaneously. Here again, injections of the inhibitor significantly reduced the ^{14}C-histamine excretion in the period when the deficiency of pyridoxine alone did not cause any further reduction in the formation of histamine. In these experiments α-methyl-histidine appears to act directly on the enzyme centre and not on the co-enzyme pyridoxal-5-phosphate, particularly because it does not inhibit the formation of 5-HT, as indicated by the excretion of 5-HIAA, to the production of which amine pyridoxal-5-phosphate is known to be a co-enzyme.

Injections of α-methyl-histidine in the amounts stated did not cause detectable psychical or physical ill effects, this in contrast to semicarbazide superimposed on the deficient diet which may elicit states of hyperirritability and panic, and in varying degrees a general deterioration of the physical state of the animal.

Finally, the effects of α-methyl-3,4-dihydroxyphenylalanine (α-methyl-DOPA) were similarly examined. In rats on adequate diet this compound in doses of 100–200 mgm./kgm., injected 4 times daily for four days, caused slight (about 25 per cent), or inconsistent, reductions in urinary histamine. In cases where the inhibition was definite, the urinary excretion of 5-HIAA was reduced to about the same extent as urinary histamine. Injections of α-methyl-DOPA caused prostration, diarrhoea, loss of appetite and body-weight.

In conclusion, α-methyl-histidine appears a promising weapon in further investigations of the physiology of histamine.

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