Inhibition of histidine decarboxylase in rat stomach by aminoguanidine

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Aminoguanidine is a potent and specific inhibitor of diamine oxidase and has been used extensively in studies on histamine metabolism (Buffoni, 1966). One of the consequences of inhibition of diamine oxidase is an increased circulating concentration of histamine, and aminoguanidine is potentially a useful drug for investigating, *in vivo*, the proposed feedback coupling between histamine and its synthesizing enzyme in the gastric mucosa of the rat (Kahlson, Rosengren & Thunberg, 1967).

A single dose of aminoguanidine (20 mg/kg) administered subcutaneously into female Sprague-Dawley rats weighing 175–200 g reduced the diamine oxidase activity of the small intestine by more than 95%. Monoamine oxidase activity in the same tissue and histidine decarboxylase in the gastric mucosa were not affected by this treatment. Administration of aminoguanidine (20 mg/kg daily) over a period of 5 days, however, reduced the histidine decarboxylase activity in the glandular stomach by more than 50%. Furthermore, the histamine content of this tissue was increased from 19·7±8·8 to 36·5±9·2 (mean±S.D. five animals). Diamine oxidase activity in the intestine remained low and monoamine oxidase was not inhibited by aminoguanidine.

To determine the effect of inhibition of diamine oxidase on the uptake of histamine, animals were pretreated with aminoguanidine for 5 days and 4 h after the last dose, 10 μ Ci ^{14}C-histamine, was injected subcutaneously. Tissues were removed 30 min later and the ^{14}C-histamine determined by isotope dilution. Aminoguanidine increased the uptake of ^{14}C-histamine in all the tissues examined. The increase was greatest in the small intestine (approximately 10-fold) and least in the brain (approximately 2-fold). There was a 6-fold increase in the uptake of ^{14}C-histamine by the glandular stomach. These results imply that, after administration of aminoguanidine over an extended period of time, a significant proportion of the histamine in the rat stomach represents that taken up from the circulation.

In the normal rat pentagastrin (200 μg/kg) or insulin (5 U/kg) produced a 4-fold increase in histidine decarboxylase in the stomach in 4 hours. This response was not affected by prior treatment with a single dose of aminoguanidine given 1, 4 or 24 h before the stimulus. In rats pretreated for 5 days, however, the response to pentagastrin was reduced by more than 60%, whereas the response to insulin was not affected. The ability of histidine decarboxylase to respond normally to pentagastrin administration when the concentration of endogenous histamine is substantially increased suggests that, under certain conditions, histidine decarboxylase may not be subject to feedback control.

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