Monoamine Oxidase Inhibitors and the Cheese Effect

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The behavior of inhibitors of monoamine oxidase-A (MAO-A) is considered in terms of the possibility of having an effective antidepressant that does not give rise to hypertensive interactions with dietary tyramine. Studies with punch-biopsy samples of human intestine and rat intestinal samples show MAO-A to be the predominant form of the enzyme in both species. Transport studies with everted rat intestinal preparations indicate that tyramine is extensively metabolized during transport through the intestine. Selective inhibition of MAO-A by clorgyline results in a large increase in the amount of unchanged tyramine transported, whereas selective inhibition of MAO-B with L-deprenyl (selegiline) has no significant effect. The behavior of reversible MAO-A inhibitors can significantly reduce, but not entirely eliminate, these effects on the intestinal metabolism of tyramine, but only if the inhibition is competitive in nature.

KEY WORDS: Tyramine; monoamine oxidase-A (MAO-A); intestine; clorgyline; L-deprenyl; brofaromine; moclobemide.

INTRODUCTION

Much of Merton Sandler's work has been devoted to the catabolism of monoamines and, in particular, to the actions and interactions of the monoamine oxidase inhibitory antidepressants. As a tribute to his wide ranging, research contributions, this paper will consider recent developments in the design of monoamine oxidase inhibitors as antidepressants.

The first generation of monoamine oxidase inhibitory antidepressants were hydrazine derivatives. These were irreversible and non-selective inhibitors of the enzyme. Although they were effective antidepressants, their use was restricted because of reports of hepatotoxicity (see 1) and adverse interactions with foods and beverages containing amines such as tyramine. Because tyramine was found to be present in relatively high concentrations in some cheeses, this latter interaction is often termed the "cheese reaction". The hypertensive response that may occur if patients treated with monoamine oxidase inhibitors (MAOIs) ingest foods or beverages containing tyramine can be fatal (see 1-5). Because of the widespread occurrence of tyramine in foods and beverages (see 4-8) patients being treated with such MAOIs had to be extremely circumspect about their eating habits. The quantities of tyramine present in foods can be extremely variable (4-6) and thus there is a risk that a patient treated with a monoamine oxidase inhibitor may experiment and find no great adverse effects, only to consume a tyramine rich sample at a later stage.

With the discovery that there were two forms of monoamine oxidase (MAO-A and MAO-B) with different substrate specificities and inhibitor sensitivities there were hopes that a selective inhibitor of one of the enzymes might prove to be an effective antidepressant with a reduced cheese reaction. Since tyramine, as well as noradrenaline and dopamine, are substrates for both forms of the enzyme in human brain, whereas 5-hydroxytryptamine (5-HT) is a substrate only for MAO-A (for reviews see 1,9), it was thought possible that a selective inhibitor of that enzyme form might sufficiently elevate the central concentrations of these neurotransmitter amines to give an antidepressants effect whilst leaving adequate
capacity for the peripheral metabolism of ingested tyramine. Although the MAO-B inhibitor deprenyl (selegiline) did not give rise to a significant cheese reaction, it was found not to be an effective antidepressant (for review see 1). In contrast, although MAO-A inhibitors, such as clorgyline, were effective antidepressants, their hypertensive interactions with dietary tyramine were similar to those of the non-selective MAO inhibitors.

EXPERIMENTAL PROCEDURE

Monoamine oxidase activity was assayed radiochemically (10) and transport studies in everted rat intestines (11) were performed as previously described. The sources of materials, analytical methods and other procedures used are also described in those publications.

RESULTS AND DISCUSSION

The observation that MAO-B inhibitors do not precipitate a significant cheese reaction can be attributed to MAO-A being the predominant form in the intestine (11,12). Figure 1 shows the distribution of the two forms of MAO in the rat intestine.

In the human intestine determinations of kinetic parameters in punch-biopsy samples gave $K_m$ values of 95 $\mu$M and 172 $\mu$M for MAO-A and -B, respectively, and the corresponding maximum velocities were 71 and 29% of the total MAO activities (11). From these values, the contributions of the two forms to the oxidation of tyramine can be calculated, as shown in Figure 2.

The predominant role of MAO-A in the oxidation of tyramine by the intestine has been shown by the measurement of the effects of selective inhibitors on the metabolism of this amine during its transport through everted rat intestinal preparations (11). Figure 3 shows the effects of treatment with amine oxidase inhibitors on the transport and metabolism of tyramine in such preparations. In the absence of inhibitors and at a concentration of 150 $\mu$M tyramine, very little (16 $\pm$ 3%) escapes metabolism during its transport through the intestine.