Does Increasing the Lipophilicity of Peptides Enhance Their Nasal Absorption?

To the Editor:

Previous communications from our laboratory and others concluded that the low bioavailabilities of nasally administered peptides are due, in part, to peptidase-catalyzed hydrolysis in the nasal cavity.\textsuperscript{1-6} We and others have demonstrated the existence of peptidase enzyme systems in the nasal cavities of both animals and humans,\textsuperscript{1-6} and we have shown that the types of hydrolyses produced by these systems may vary greatly among species.\textsuperscript{5}

On the other hand, it has been demonstrated that the small amounts of peptides that cross the nasal membrane in rats do so at a very rapid rate.\textsuperscript{7-8} Thus, the systemic bioavailability of a nasally administered peptide is the result of two rapid and competing kinetic processes: absorption and hydrolysis.\textsuperscript{6}

It should be possible to minimize hydrolysis and improve bioavailability by accelerating the absorption process so that a greater fraction of the peptide follows the absorption pathway. Some workers have attempted to accomplish this through the use of absorption enhancers,\textsuperscript{9,10} but many of these compounds are irritating to the nasal mucosa.\textsuperscript{11} Another approach is to increase the lipophilicity of the peptide so as to improve its penetration into the nasal membrane.

This communication reports on the comparative partition coefficients, in vitro hydrolysis rates, and the rates of disappearance from rat nasal washings of the small peptide L-tyrosyl-L-tyrosine (LTLT) and its methyl ester (LTLTME). The analytical method was similar to those described previously,\textsuperscript{1,5,6} and the rates of hydrolyses of the compounds were determined in washings from the rat nasal cavity using a technique described previously.\textsuperscript{1}

The oil-water partition coefficients in the n-octanol: pH 7.4 phosphate buffer system were 0.02 for LTLT and 3.2 for LTLTME. The rates of hydrolyses of LTLT and LTLTME in rat nasal washings were very similar (see Figure 1), suggesting that the peptidase enzyme systems of the rat nasal cavity have about the same affinity for the two compounds. This also suggests that hydrolysis could be responsible for significant loss of the compounds from the rat nasal cavity during the in vivo—in situ experiments.

It has previously been shown that the rates of hydrolysis of peptides, in particular LTLT, in rat nasal enzyme systems are concentration dependent.\textsuperscript{4,12} Therefore, we studied the disappearance of LTLTME from the rat nasal cavity at various concentrations to determine the most advantageous concentration(s) at which to compare the absorption rates of the two compounds.

The results shown in Figure 2 indicate that the disappearance of LTLTME from the rat nasal cavity was slowest at 40 mM and was almost as slow at 8 mM. At 40 mM, the fraction of LTLTME that was converted to tyrosine (by hydrolysis of the peptide bond) was 0.1 times that at 2 mM. There was no evidence of hydrolysis of the methyl ester at any concentration. These results suggest that the rat nasal peptidases become saturated at \textasciitilde 8 mM LTLTME. Therefore, to minimize hydrolysis during the in vivo—in situ experiments, it was decided to study both compounds at concentrations at which the nasal peptidases were saturated. For LTLT, the concentration was limited to 13.4 mM by its solubility; however, this concentration exceeded the concentration at which the peptidase enzymes were saturated.

Figure 3 shows the comparative rates of overall disappearance of LTLTME and LTLT from the rat nasal cavity using the in vivo—in situ technique. Since the absorption rate constant for passive diffusion is concentration independent, whereas rat nasal peptidases are inhibited at the high concentrations employed (see Figure 2), it can be safely...
assumed that virtually all the disappearance from this system was due to passive absorption. These results show that the rates of passive absorption of these two similar peptides are identical, despite the fact that there is a 160-fold difference in their partition coefficients.

These preliminary results suggest that enhancing the lipophilicity of a peptidase-labile peptide would probably not have any great effect on its bioavailability from the nasal cavity. Thus, costly product development efforts utilizing this approach may have little chance of success.

References and Notes


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