Stereochemical Considerations in Structural Comparison of Enkephalins and Endorphins with Exogenous Opiate Agents

Keyphrases □ Stereochemistry—enkephalins and endorphins compared to endogenous opiates □ Methionine-enkephalin—stereochemistry compared to exogenous opiates □ Morphine—stereochemistry compared to enkephalins and endorphins □ Enkephalins—stereochemistry compared to exogenous opiates □ Opiates—stereochemistry compared to enkephalins and endorphins

To the Editor:

The existence in mammalian species of endogenous peptides, such as methionine-enkephalin (I), which act as ligands for opiate receptors, has generated considerable interest (1–3). The morphine-like properties of these peptide ligands lead to the question of their structural relationship with morphine (II) and congeneric opiates (4–9).

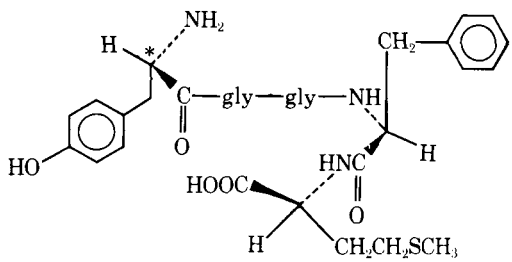
The resemblance between the primary structure of I and, for example, (−)-morphine (II), by virtue of their β-(4-hydroxyphenyl)ethylamine units, was discussed previously (6). (In Structures I and II, the * denotes the α-position of the tyramine unit. The absolute configurations for the asymmetric centers are all *S* for I and 5*R*, 6*S*, 9*R*, 13*S*, and 14*R* for II.) However, discrimination between enantiomeric ligands by the chiral macromolecular complex known as the opiate receptor is not addressed in an elementary tyramine relationship, which relies on the spatial arrangement of two interaction sites, the phenyl and amino functionalities, in an effectively achiral (10) tyramine unit. Comparison of I and II demonstrates that, in superimposing the amino and phenyl groups, α-substituents on the tyramine moieties are not congruent. (−)-L-Tyrosine has the *S*-configuration and (−)-morphine has the 9*R*-configuration (11–14), representing, in real terms, an opposite spatial distribution of functionality at this stereocenter.

Is the absolute stereochemistry of the 9*R* center in II and its congeners important for receptor binding and/or pharmacological activity? Among morphine-like structures, one enantiomer is commonly much more active than its counterpart (11, 12). Where the absolute stereochemistry is known or implied, the same configuration is found at the α-carbon of the tyramine unit (13–19), exemplified by a number of morphinan and 6,7-benzomorphan analgesic agonists and/or antagonists: II, (−)-3-hydroxy-*N*-methylisomorphinan (20), (−)-butorphanol (21), levorphanol, levallorphan, (−)-etorphine, (−)-nalorphine, and (−)-cyclazocine (22); as a series, these compounds have other portions of their structures, remote from the tyramine segment, grossly altered. The known correspondent enantiomers exhibit relatively little or no analgesic activity: *e.g.*, (+)-morphine, (+)-3-hydroxy-*N*-methylisomorphinan (20), (+)-cyclazocine (22), (+)-butorphanol (21), dextrophan, and (+)-3-hydroxy-*N*-allylmorphinan, and/or minimal binding (23) to receptor tissue (brain): *e.g.*, (+)-3-hydroxy-*N*-allylmorphinan and dextrophan. Thus, it seems that the stereochemistry at the α-tyramine carbon atom is specifically significant.

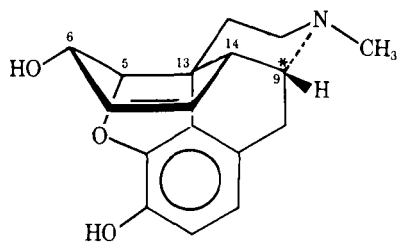
If a morphological comparison of II and I is deemed valid (4–9), then cognizance of the enantiomorphism of the tyramine segment becomes vital to arguments relating their structural characteristics. Thus, we were concerned that two groups of researchers (7–9) employed incorrect steric relationships to correlate the structures of I and II, improperly achieving coincidence of the phenyl, amino, and side chain [so-called three-point contact (8)] and simultaneously establishing an erroneous structure–activity pattern. One group of collaborators compared the structure of II with unnatural, all-D-I in one paper (7) and inactive (+)-morphine with natural I in another paper (8); Jones *et al.* (9) employed (+)-morphine in their comparison. Other investigators (4–6, 24) utilized correct stereostructures in their discussions[1]. In any case, the importance of chirality in relating the morphology of morphine-like opiates and of the enkephalins has never been explicitly enunciated.

Conformational factors for I are also important in the correlation of endogenous and exogenous opiate substances. For example, the absence of, or reduction in, activity for the enkephalin fragments tyr-gly-gly-phe (25) and tyr-gly-gly (26) and for the diastereomeric pentapeptide tyr-gly-gly-(D)-phe-met (9, 27) necessitates consideration of the nontyrosine amino acids of I and their conformational disposition (27, 28). At present, conflicting results exist with respect to the secondary structure (conformation) of I in solution, as determined spectroscopically (7, 9, 29, 30), so no definitive statement can be made on this point.

One can still acknowledge the first-order "tyramine"



I



II

[1] To eliminate potential confusion, we wish to point out that the stereostructures given for (−)-morphine in "Principles of Drug Action," by A. Goldstein, L. Aronow, and S. M. Kalman (Wiley, New York, N.Y., 1st and 2nd eds., 1968 and 1974, pp. 53 and 34, respectively) are those of the analgesically inactive enantiomer (+)-morphine.

hypothesis (6) and the lack of correspondence of absolute stereochemistry at the α-carbon of the tyramine unit, the importance of which is reinforced by the virtual lack of activity (mouse vas deferens) of the D-tyr[1] derivative of I[2] (27, 31). The structure–activity relationship between I and II is thus marked by a reversal in stereospecificity. An analogous reversal (by enantiomorphism at the α-carbon stereocenter of a β-phenethylamine unit) occurs in the analgesics (−)-*N,N*-dimethyl-1,2-diphenylethylamine[3] (*R*-configuration) (32) and (+)-1-cyclohexyl-4-(1,2-diphenylethyl)piperazine[4] (*S*-configuration) (33).

Stereochemical inversions in structure–activity relationships are also exhibited in diphenylpropylamine (methadone-type) and certain anilide analgesics and may generally be interpreted in terms of differing substrate–receptor interactions (11, 34) and/or induced-fit theories (35). Recent suggestions (36) of opiate receptor heterogeneity (κ, μ, δ) are especially apropos to this latter stereochemical discussion and have relevance to a comparison of II and the enkephalins, given their stereochemical noncorrespondence.

Any model proposing to rationalize the structure–activity relationships of opiates must consider stereochemical inversion phenomena[5]. If the "tyramine" relationship mentioned is valid, then difficulties arise in defining a structure–activity relationship for II (and its analogs) and, *e.g.*, I.

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[2] Also, D-tyr[1]-β_c-endorphin has minimal opiate activity (ileum assay) and analgesic potency compared to natural β_c-endorphin [see D. Yamashiro, L.-F. Tseng, B. A. Doneen, H. A. Loh, and C. H. Li, *Int. J. Peptide Protein Res.*, **10**, 159 (1977)].

[3] Spa.

[4] MT-45.

[5] A recent, simplistic model to explain structure–activity relationships of opiate agents unfortunately ignored absolute stereochemical factors [see A. P. Feinberg, I. Creese, and S. H. Snyder, *Proc. Natl. Acad. Sci. USA*, **73**, 4215 (1976)].

Absolute Drug Bioavailability II: Evaluation of Renal Clearance Perturbation Method Using Literature Data Assuring a Fraction Absorbed of Unity

Keyphrases □ Bioavailability, absolute—evaluation of renal clearance perturbation method using literature data assuring a fraction absorbed of unity □ Renal clearance—perturbation method evaluated using literature data assuring a fraction absorbed of unity

To the Editor:

Three years ago, a technique allowing an estimation of the absolute bioavailability of a drug without reference to a parenteral dose was reported (1). Since that time, two other reports (2, 3) suggested that this method is useful and reasonably accurate. However, the procedure has not been tested using data where the fraction absorbed is known. This communication reports the results of the application of the previously described technique to recently reported furosemide pharmacokinetic data obtained following intravenous administration.