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Letters to the Editor

Proposal regarding opioid anomalies

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Opioid activity associated with the (+)-isomer of a structurally rigid molecule such as a 3-benzazocine (6,7-benzomorphan) is considered abnormal. However, extensive studies of the optical isomers of 1,2,3,4,5,6-hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocine-8-ol (metazocine) and certain of its homologues, revealed a remarkable profile of activity (Fraser et al 1962; Ager et al 1969; Kosterlitz 1969; Villarreal 1970). It was found that the (−)-isomers had potent antinociceptive activity in the hot-plate assay and precipitated abstinence in morphine-dependent monkeys. On the other hand, four of the five corresponding (+)-isomers also had antinociceptive properties in mice. Indeed, although the (+)-isomers were always less potent than their respective enantiomers, the difference was as little as six-fold for the 6,11-diethyl compound. Interestingly, the (+)-isomers were all inactive as antagonists and all of the homologues with ethyl or propyl groups at carbon 6 substituted for morphine in addicted monkeys. Thus, these active (+)-isomers were clearly manifesting what has been designated as mu opioid properties.

Although a rather ingenious opioid receptor model which explained similarities in pharmacological properties of opioids with apparently dissimilar chemical structures was proposed (Feinberg et al 1976), and this model could help understand certain stereochemical paradoxes, the issue of antipodal (enantiomeric) anomalies was not addressed. In an attempt to explain certain stereochemical abnormalities, another worker modified this model (Galt 1977). The modification involved an extension of the planar binding site (A) rather than the presence of an additional lipophilic region (F) of the model.

Knowing that there is a spectrum of activity ranging from absolute stereospecificity for the optical isomers of morphine to anomalous activity for the optical isomers of metazocine and its homologues, and because we felt that some explanation must exist, we decided to build Dreiding models of the antipodes of metazocine and morphine, and of enantiomers of the morphinan series levorphanol and dextrorphan to determine firsthand what features they had in common or for that matter how they were dissimilar. Once the stereomodels of metazocine were built, we noted that the piperidine rings of (+)- and (−)-metazocine (Figs 1 and 2, respectively) could be superimposed (Fig. 3) and that as a result, the following carbon atoms were juxtapositioned; namely, (+)- and (−)-7, (+)- and (−)-8

* Correspondence.

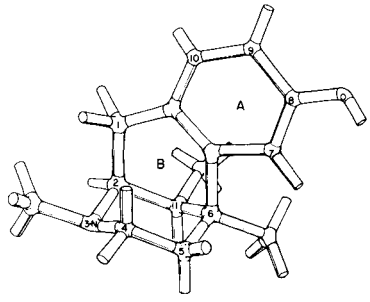

FIG. 1. Perspective side view drawing of (+)-metazocine.

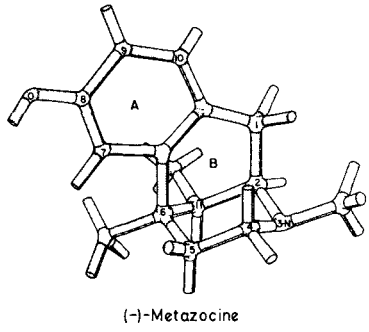

FIG. 2. Perspective side view drawing of (−)-metazocine.

(including the hydroxy groups), and (+)- and (−)-6 (plus the methyl groups). The major difference was the orientation of rings A and B. As shown in Fig. 3, rings A and B (comparable to those in morphine) of (+)-metazocine appear to be nearly hinged, as it were, to rings A and B, respectively, of (−)-metazocine by carbons 6, 7 and 8. These rings gradually diverge from one another so that the widest separation between rings A is 1·5 Å and the widest separation between rings B is 2·0 Å. Also, the methyl groups at carbon 11 are pointed in different directions. Since (+)-metazocine (6,11-dimethyl) shows no agonist activity and the (+)-6,11-diethyl and propylmethyl homologues are the most potent regarding antinociception in mice and substitution for morphine in addicted monkeys, and since all the homologues studied are devoid of antagonist activity, the ethyl and/or propyl substitutions of the molecule must be important for agonist activity. Considered another way, if the piperidine ring of (+)-6,11-dialkyl-metazocine is superimposed on the piperidine ring of (−)-morphine, it can be determined that the ethyl and propyl (alkyl) chains at carbon 6 of metazocine and homologues can rotate in the region of ring C of morphine. In another series known as the *N*-methyl phenylmorphans (3-hydroxyphenyl-*N*-methylmorphan) both antipodes are potent analgesics. The (+)-enantiomer had a high dependence liability in monkeys whereas the (−)-isomer exhibited weak narcotic antagonist properties and a mild dependence-producing capacity (May & Takeda 1970; Cochran 1974; Rogers &

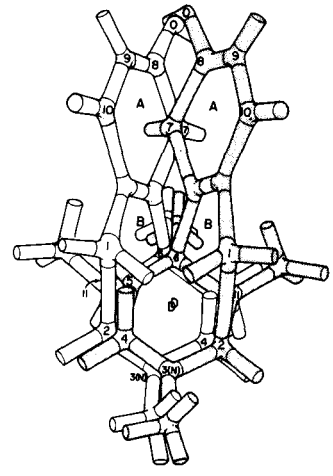

FIG. 3. A top view (+)- and (−)-metazocine with piperidine rings superimposed one upon the other. (−)-Metazocine shown in grey.

May 1974; Awaya et al 1984). In this series, the position of the phenyl group in space relative to the nitrogen atom is equatorial rather than axial, as in metazocine. However, we superimposed the piperidine rings of this phenylmorphan and morphine. Then, a portion of the phenyl ring of the phenylmorphan molecule encroached on a portion of ring C of (−)-morphine, again showing the importance of ring C. This is in contrast to the proposal (Feinberg et al 1976) that the phenyl ring of a phenylmorphan interacts with region F of their model.

Equally important, as only the (−)-homologues of metazocine have antagonist properties and the (+)-isomers of 6,7-benzomorphans with *N*-dimethylallyl or cyclopropylmethyl substituents such as pentazocine or cyclazocine are always much less potent as antagonists (Aceto et al 1969), it would seem that the orientation of the methyl group at carbon 11 and/or of rings A and B is relatively important regarding antagonist activity. To appreciate this, it is necessary to indicate that opioid receptor models stress that antagonist activity is associated, for the most part, with the *N*-substituent which is usually either a three carbon chain or a methylene group linked to a small cycloalkyl ring. That many *N*-methyl substituted compounds have antagonist properties is usually overlooked.

Once we realized that the Dreiding models of benzomorphans helped resolve these anomalies, we reasoned that models of natural and unnatural morphine, and for that matter dextrorphan and levorphanol, would also be revealing. With (+)- and (−)-morphine (Figs 4, 5, respectively), we demonstrated that the piperidine rings could be superimposed (Fig. 6), that carbon atoms 3, 4 and 13 of (+)-morphine would then align themselves with carbon 3, 4, 13 respectively of natural morphine. In addition, the oxygen bridges overlapped. Rings A and B would also

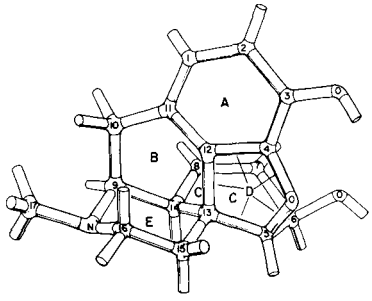

FIG. 4. A depiction of (+)-morphine (side view).

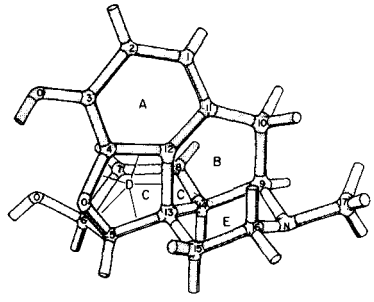

FIG. 5. A depiction of (−)-morphine (side view).

align themselves as described above for metazocine, and importantly, rings C would project in opposite directions (see Fig. 6). Models of dextrorphan and levorphanol (not shown) were in many respects similarly revealing. It is rather surprising that dextrorphan has relatively weak analgesic properties compared with levorphanol if we consider that two apparently important functional moieties are present, namely, the superimposable piperidine rings in conjunction with closely aligned aromatic rings A. *Apparently, the proper orientation of ring C is crucial.* A similar argument could be presented to account for the differences beween natural and unnatural morphine.

Morphine is believed to interact as an agonist not only with mu receptors but also to a lesser extent, with kappa receptors. The mu receptors seem to be involved in the production of a number of actions including supraspinal analgesia and physical dependence. As ring C or certain ring fragments (6-ethyl or propyl of the benzomorphan series) are associated with mu activity and compounds which lack these elements are classified as kappa agonists and mu antagonists (such as pentazocine), we speculate that ring A, in conjunction with ring B of natural morphine, are important structural features for these prototypical agonist/antagonists. Finally, it is evident that studies with racemates may be misleading and that, whenever possible, enantiomers should be used especially if theoretical models are being proposed.

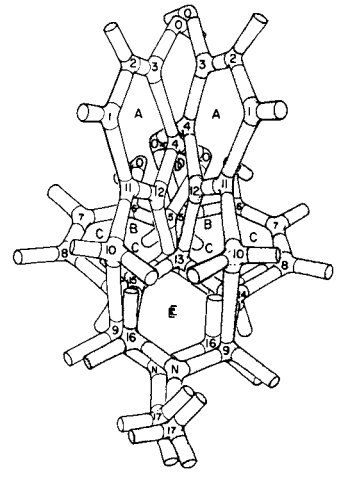

FIG. 6. A perspective top view of natural morphine (shown in grey) and unnatural morphine with piperidine rings superimposed.

In conclusion, Dreiding optical stereomodels have provided a possible explanation for the so-called anomalous activity exhibited by enantiomers of metazocine and its homologues and *N*-substituted phenylmorphans. They also provide evidence that the area around ring C of natural morphine is crucial for mu agonist activity. We also speculate regarding the structural requirements of kappa agonist and mu antagonists of the *N*-substituted opioids. Caution is urged regarding the interpretation of results of studies conducted with racemates.

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