Relationships between Opiate Receptor Binding and Analgetic Properties of Prodine-Type Compounds

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The receptor binding affinities of some diastereoisomeric prodine analogues have been compared with their analgetic activities determined by the hot-plate test in mice. The close correlation found between these potencies indicates that the relative analgetic activities of the α/β isomers are determined primarily by the appropriate association to the receptor sites.

In the course of our studies on the influence of geometrical isomerism upon analgetic activity of α- and β-prodine-type compounds, it has been demonstrated recently that, except for the pair with a C-3 Me substituent, the trans 3-R/4-Ph geometry rather than the cis geometry leads to more active isomers.1 Assignment of the configuration trans to α and cis to β isomers was based on chemical studies and the 1H NMR characteristics of isomeric esters.1,2

The greater analgetic activity of the α form when R ≠ Me, could be related to events at the receptor sites or to differences in transport and distribution of the compounds. In the present study we have investigated the affinity of binding of some isomeric pairs (1-4) to opiate receptors from rat brain homogenates.

The affinities of α- and β-prodine-type compounds for the opiate receptor, compared with their analgetic activities in vivo, are summarized in Table I. The K values represent the concentration required to displace 50% of the specifically bound [3H]dihydromorphine and it is an estimate of the apparent dissociation constant of the analgesic–receptor complex under the experimental conditions used.4 By plotting the log of ED₉₀ (nM/kg) against the corresponding log of K (nM), all the points (except β-4) were on a straight line, whose slope (s = 1.16) and linear correlation coefficient (r = 0.99; n = 7), calculated by the method of least squares, were close to unity (Figure 1).

These results indicate that there is almost complete correspondence of analgetic potency with receptor affinity in this class of piperidines. Further this relationship reveals that differences due to absorption, distribution, and metabolism should be minimal in these isomeric pairs.

The high receptor affinity found for the allyl isomer α-3 emphasizes the association of the equatorial allyl group to an additional binding site of the receptor.2,5 The enhanced affinity displayed by the more potent enantiomer (+)-α-3 confirms the stereoselectivity of the opiate receptors.6 The hexyl derivative β-4 showed a very weak analgetic activity, poorly dose-related (Table I), and its relatively high affinity for the receptor may be due to some weak antagonist property that the C-3 hexyl group confers to the molecule in the same way as C₅-C₇ N-alkyl chains do in the ketobemidones, an analogous class of piperidine compounds.7 The hexyl derivative α-4, which was inactive as an analgetic in the hot-plate test (Table I), competed with [3H]dihydromorphine for receptor binding at a high concentration (10⁻⁴ M), but in contrast to all the piperidines tested, it displaced both specifically and nonspecifically bound [3H]dihydromorphine, as Klee and Streaty found for some tranquilizers or pseudocholinesterase inhibitors.8

From the results here reported it seems reasonable to assume that changes in analgetic activity seen in the α/β pairs may be clearly related to receptor interaction. The β configuration appears to be superior to the α configuration only when the C-3 axial substituent is a methyl group (1). However, with lengthening of the side chain (2, 3) it is the α configuration, with an equatorial C-3 substituent, which better fulfills the steric requirement of the receptor.

Experimental Section
Syntheses and configurations of the piperidines tested were reported previously.1 The [7,8-³H]dihydromorphine (specific activity 51.2 Ci mmol⁻¹) was obtained from New England Nuclear Corp. The material was stored after dilution with 0.32 M sucrose to a concentration of 10⁻⁶ M at -20 °C. All operations involving [³H]dihydromorphine were carried out in darkness or in very dim, indirect daylight because of the photosensitivity of this compound.8

Binding experiments were carried out as described by Klee and Streaty.4 Rat brain homogenates were prepared in 0.32 M sucrose

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Table I. Opiate Receptor Affinities and Analgetic Activities of Prodine-Type Compounds

<table>
<thead>
<tr>
<th>Compdδ</th>
<th>Receptor affinity</th>
<th>ED₉₀, mg/kg sc, in mice,ε</th>
<th>Hot-plate limits (95% confidence limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-1</td>
<td>80</td>
<td>0.92 (0.73-1.17)</td>
<td></td>
</tr>
<tr>
<td>β-1</td>
<td>20</td>
<td>0.18 (0.13-0.23)</td>
<td></td>
</tr>
<tr>
<td>α-2</td>
<td>40</td>
<td>0.40 (0.30-0.60)</td>
<td></td>
</tr>
<tr>
<td>β-2</td>
<td>200</td>
<td>3.5 (2.5-4.5)</td>
<td></td>
</tr>
<tr>
<td>(+)-α-3</td>
<td>6</td>
<td>0.03 (0.02-0.04)</td>
<td></td>
</tr>
<tr>
<td>α-3</td>
<td>400</td>
<td>11.7 (9.4-14.6)</td>
<td></td>
</tr>
<tr>
<td>α-4</td>
<td>e</td>
<td>Inactive at 80</td>
<td></td>
</tr>
<tr>
<td>β-4</td>
<td>100</td>
<td>54.4 (14.9-198.8)</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>3</td>
<td>1.2 (0.9-1.3)</td>
<td></td>
</tr>
</tbody>
</table>

δ All compounds were administered as HCl salts. b Expressed as the concentration required for 50% inhibition of specific binding of [³H]dihydromorphine. ε Reference 1. This specimen was obtained from Profesor P. S. Portoghese (ref 5) through Dr. May's collection. ε This compound, at high concentration (10⁻⁴ M), displaces both specifically and nonspecifically bound [³H]dihydromorphine. f Poorly dose-related response.
The value for analgetic response from log assay tube which also contained the substance to be tested as line because this compound showed a very poorly dose-related analgetic activity. The substituents chosen were those which often enhance this activity of 6,7-benzomorphans.3

Three 1,3-dimethyl-9-hydroxy-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine derivatives (7-9) have been synthesized and tested as analgesics. The synthesis of these compounds involved conversion of 1-methyl-7-methoxy-β-tetralone (1) by Mannich reaction with MeNH2 and HCHO to give the 11-ketone 2, from which 7, 8, and 9, respectively, were obtained. These compounds have analgesic activity, and was achieved by Mannich reaction with MeNH2 and HCHO in one step. The carbonyl group in 2 was reduced to methylene by Wolff-Kishner reaction, giving compound 3. On the other hand, ketone 2 was treated with Ph3P==CH2 to give the 11-methylene compound 4. Hydrogenation of 4 over Pt catalyst in EtOH gave 11α-methyl

9-Hydroxy-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine Derivatives as Analgesics

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Three 1,3-dimethyl-9-hydroxy-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine derivatives (7-9) have been synthesized and tested as analgesics. The synthesis of these compounds involved conversion of 1-methyl-7-methoxy-β-tetralone (1) by Mannich reaction with MeNH2 and HCHO to give the 11-ketone 2, from which 7, 8, and 9, respectively, were obtained. These compounds have analgesic activity, and was found to be comparable to codeine.

Chemistry. Conversion of 1-methyl-7-methoxy-3,4-dihydro-2(1H)-naphtaleneone (1) to the desired framework 2 was achieved by Mannich reaction with MeNH2 and HCHO in one step. The carbonyl group in 2 was reduced to methylene by Wolff-Kishner reaction, giving compound 3. On the other hand, ketone 2 was treated with Ph3P==CH2 to give the 11-methylene compound 4. Hydrogenation of 4 over Pt catalyst in EtOH gave 11α-methyl