Abstract

Mu opioid receptor (\(\mu\); MOR): activation kills pain; over time, the body desensitizes to this effect, becomes tolerant.\(^{1}\)

Delta opioid receptor (\(\delta\); DOR): inhibition prevents tolerance to MOR agonists.\(^{2}\)

Naltrindole (NTI) is a selective DOR antagonist that blocks the development of tolerance to MOR agonists such as morphine.\(^{3}\)

NTI does not block any anagistic effects of morphine because it only blocks the delta receptor; it can not bind into the mu receptor binding pocket.

The delta opioid receptor recognizes NTI and becomes inhibited. Understanding how delta recognizes antagonists is very important when we want to design a single compound that activates mu (like morphine), and inactivates delta (like naltrindole).

MOR and DOR

\[
\begin{align*}
\text{MOR} & \quad \text{mu receptor} \\
\text{DOR} & \quad \text{delta receptor}
\end{align*}
\]

\[
\begin{align*}
\text{Mu opioid receptor} & \quad \text{N-substituent: determines agonist or inhibitor (agonist/antagonist)} \\
\text{Morphine agonist} & \quad \text{OxyContin antagonist}
\end{align*}
\]

"Indole Ring"

\[
\begin{align*}
\text{Alpha Helices} & \quad \text{Yellow} \\
\text{Beta Sheets} & \quad \text{Crimson Blue} \\
\text{Non-Motif Backbone} & \quad \text{Blue} \\
\text{Asp147} & \quad \text{Lime} \\
\text{Tyr148} & \quad \text{Purple} \\
\text{Lys233} & \quad \text{Hot Pink} \\
\text{His297} & \quad \text{Chocolate}
\end{align*}
\]

\[
\begin{align*}
\text{Oxymercine} & \quad \text{MOR agonist} \\
\text{Morphine} & \quad \text{MOR agonist} \\
\text{Naltrindole} & \quad \text{DOR antagonist}
\end{align*}
\]

\[
\begin{align*}
\text{alpha} & \quad \text{rigid, bulky group: thought to determine DOR selectivity}
\end{align*}
\]

The Problem?

Morphine Prescribed for Pain Relief

The Problem? Tolerance Develops

Potential Solution Morphine + Naltrindole

Pain is a significant public health problem that costs society at least $560-$635 billion annually (an amount equal to about $2,000.00 for every person living in the United States.

In 2011, at least 100 million adult Americans have common chronic pain conditions, a conservative estimate because it does not include acute pain or chronic pain in children.

In 2008 the cost to federal and state governments of medical expenditures for pain was $99 billion.

The Next Frontier: BOM (UMB246)

A single compound that simultaneously activates MOR and deactivates DOR to treat chronic severe pain could lower health care costs and benefit patients. This was the rationale behind the development of UMB246.

In 1992, the Portuguese group at the University of Minnesota made benzylidenenaltrexone (BNTX), which was a DOR, antagonist with modest selectivity over MOR. Because most N-methyl opioids are mu agonists, researchers at the University of Maryland hypothesized that placement of the N-group of the N-methyl with an N-methyl would produce a MOR agonist.

Additionally, the benzylidine group was hypothesized to be flexible enough to allow binding to MOR. The result is benzylidenoxymorphine (BOM, UMB246), a new small molecule MOR partial agonist/DOR antagonist structural scaffold.

Cell types expressing each opioid receptor subtype were obtained from Dr. Larry Toll (SRU International, Mariol Park, CA). Competitive binding experiments were performed in the laboratory of Prof. R. Matsunoto (West Virginia University). Table 1 shows UMB246 binds similarly well to MOR and DOR, and is approximately 60-fold selective over KOR.

Table 1: Percent inhibition (specific binding) of MOR, DOR, KOR.

<table>
<thead>
<tr>
<th>Compound (Name)</th>
<th>UMB</th>
<th>K (nM)</th>
<th>MOR</th>
<th>K (nM)</th>
<th>DOR</th>
<th>K (nM)</th>
<th>K (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMB246</td>
<td>246</td>
<td>17.5 ± 1.10</td>
<td>14.4 ± 0.65</td>
<td>1067 ± 39</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Laboratory Data

Both the mu opioid receptor (MOR) and the delta opioid receptor (DOR) play a crucial role in analgesia. DOR can modulate the tolerance effect resulting from prolonged administration of opiates like morphine and oxycodone (OxyContin). In order to maintain analgesic effects, caretakers must increase the dosage of an opiate administered to a patient. This is extremely expensive and can lead to various adverse side effects such as constipation and increased risk of overdose. In order to combat these side effects, chemists and pharmacologists are attempting to develop drugs that have a lessened tolerance effect; by antagonizing, or shutting off, the DOR receptor, the tolerance effect is eliminated. Naltrindole (NTI) fills this role, but unfortunately it does not agonize, or turn on, the MOR receptor, and thus has absolutely no analgesic effect by itself. Therefore, scientists are trying to develop MOR agonist/DOR antagonist drugs that would produce pain-killing effect without tolerance. Benzylidenoxymorphine (BOM, UMB246) may serve as an example of this type of compound. The purpose of this scientific exploration is to develop a solution to the chronic pain that plagues 110 million Americans and costs our nation $500 billion annually.

Conclusion


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References

1. Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education: Relieving Pain in America, a Blueprint for Transforming Prevention, Care, Education and Research. The National Academies Press, 2011, pp. 17, 102.


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