Antinociception and the New COX Inhibitors: Research Approaches and Clinical Perspectives

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ABSTRACT

New generations of cyclooxygenase (COX) inhibitors are more potent and efficacious than their traditional parent compounds. They are also safer than the classic non-steroidal anti-inflammatory drugs (NSAIDs) and are starting to be used not only for low to moderate intensity pain, but also for high intensity pain. Three different strategies have been followed to improve the pharmacological profile of COX inhibitors:

1. Development of COX-2 selective inhibitors. This is based on the initial hypothesis that considered COX-2 as the enzyme responsible for the generation of prostaglandins only in inflammation, and, therefore, uniquely responsible for inflammation, pain and fever. Initial expectations gave rise to controversial results, still under discussion. The second generation of these compounds is being developed and should contribute to clarifying both their efficacy and the specific functions of the COX enzymes.

2. Modified non-selective COX inhibitors. Molecules like nitro-NSAIDs or tromethamine salt derivatives have been synthesized considering that both COX-1 and COX-2 are responsible for the synthesis of prostaglandins involved either in homeostatic functions or inflammation. Nitroaspirin, nitroparacetamol or dexketoprofen trometamol are some examples of molecules that are already showing an important clinical efficacy. The modifications performed in their structures seem to lower the unwanted side effects as well as to enhance their analgesic efficacy.

3. Combined therapy of classic NSAIDs with other drugs. This strategy looks for improvements in the incidence of adverse effects or to take advantage of the synergistic enhancement of their therapeutic effects. Some of the molecules resulting from these strategies are very valuable as therapeutic agents and open a wide range of possibilities in the treatment of high intensity pain, including neuropathic pain, and opiate sparing therapy.

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