Tracking down the ideal analgesic

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Translated from Le Journal de Montréal, November 07, 2016

The spectacular discovery of a compound possessing an analgesic action as strong as that of morphine, but lacking its secondary effects, could revolutionize the treatment of pain.

The **opium** extracted from the somniferous poppy (*Papaver somniferum*) has been in use for over 4,000 years due to its remarkable effectiveness at diminishing pain. The alkaloids from this poppy, particularly morphine, are plant-derived molecules with the strongest known analgesic action, a property due to their ability to interact with the opiate receptors located within the central nervous system. By binding to these receptors, the opiates (substances derived from opium) and opioids (substances not derived from opium but which possess a similar analgesic action) prevent pain signals from reaching the brain and, consequently, are invaluable tools for the treatment of pain, particularly severe pains (postoperative, traumatic, advanced cancer).

However, the analgesic actions of the opiates and the opioids is not perfect, particularly when these substances are used over the long term for the treatment of chronic pains.

Aside from nausea and constipation, two frequent secondary effects, the repeated consumption of these medications over a long period can also lead to tolerance for these medications in certain persons, where progressively greater doses are required to obtain a similar effect. This tolerance can lead to dependence on, and overconsumption of, these medications which is very dangerous since the application of strong doses of opiates can cause complete inhibition of nerve signals to the lungs, causing death by respiratory arrest.

Dependence and overdose of certain opiates and opioids are actually growing quickly in several regions of North America, with no less than 19,000 Americans dead through overdose of these medications in 2014.

MOLECULAR DESIGN

The ideal analgesic should thus be a molecule which possesses anti-pain properties similar to those of opiates, but which can be used for a prolonged period without risk of dependence or of respiratory depression. A study performed by Californian scientists which recently appeared in the prestigious journal *Nature* allows us to consider whether this dream could soon become reality[1].

Several studies have shown that the positive and negative effects of opioids are due to the production of two different signals following binding to their receptor: on the one hand, the positive analgesic effect is due to activation of a protein called G_i, whereas the secondary effects (dependence, constipation, respiratory depression) are caused by activation of a protein called ß-arrestin.

The researchers therefore sought to identify compounds capable of binding to the receptor in such a way as to principally activate the positive signal (analgesia) by visualizing the interactions of over three million molecules with the receptor using computerized molecular modeling. For each compound, over a million configurations were tested in order to detect the molecules which exhibited the highest affinity, resulting in the identification of 23 strongly-binding molecules possessing a structure completely different from that of actual opiates.

A THERAPEUTIC REVOLUTION?

Even more interesting, they observed that the binding of one of these molecules (called compound 12) specifically stimulated the signal responsible for analgesia. To determine if this preferential activation was associated with a decrease in secondary effects, they compared the effects of this compound to that of morphine in animal models. They found that the new compound was as effective as morphine at diminishing pain, but that it provoked less constipation, had no impact on the respiratory activity of the animals and that the animals did not show any evidence of dependence. In other words, it was the ideal analgesic!

Subsequent studies are certainly necessary to confirm the absence of secondary effects in humans and to determine if this compound could prove to be the first member of a new generation of analgesics. One thing is certain: the innovative approach used by these scientists is very promising and could, in the short to medium term, revolutionize the treatment of pain.

(1) Manglik A et al. Structure-based discovery of opioid analgesics with reduced side effects. Nature 2016;537(7619):185-190.

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