

The pain puzzle: Uncovering how morphine increases pain in some people

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For individuals with agonizing pain, it is a cruel blow when the gold-standard medication actually causes more pain. Adults and children whose pain gets worse when treated with morphine may be closer to a solution, based on research published in the January 6 on-line edition of *Nature Neuroscience*.

"Our research identifies a molecular pathway by which [morphine](#) can increase [pain](#), and suggests potential new ways to make morphine effective for more patients," says senior author Dr. Yves De Koninck, Professor at Université Laval in Quebec City. The team included researchers from The Hospital for [Sick Children](#) (SickKids) in Toronto, the Institut universitaire en santé mentale de Québec, the US and Italy.

New pathway in pain management

The research not only identifies a target pathway to suppress morphine-induced pain but teases apart the pain hypersensitivity caused by morphine from tolerance to morphine, two [phenomena](#) previously considered to be caused by the same mechanisms.

"When morphine doesn't reduce pain adequately the tendency is to increase the dosage. If a higher dosage produces [pain relief](#), this is the classic picture of morphine tolerance, which is very well known. But sometimes increasing the morphine can, paradoxically, makes the pain worse," explains co-author Dr. Michael Salter. Dr. Salter is Senior

Scientist and Head of Neurosciences & Mental Health at SickKids, Professor of Physiology at University of Toronto, and Canada Research Chair in Neuroplasticity and Pain.

"Pain experts have thought tolerance and hypersensitivity (or hyperalgesia) are simply different reflections of the same response," says Dr. De Koninck, "but we discovered that cellular and signalling processes for morphine tolerance are very different from those of morphine-induced pain."

Dr. Salter adds, "We identified specialized cells – known as microglia – in the spinal cord as the culprit behind morphine-induced pain hypersensitivity. When morphine acts on certain receptors in microglia, it triggers the cascade of events that ultimately increase, rather than decrease, activity of the pain-transmitting nerve cells."

The researchers also identified the molecule responsible for this side effect of morphine. "It's a protein called KCC2, which regulates the transport of chloride ions and the proper control of sensory signals to the brain," explains Dr. De Koninck. "Morphine inhibits the activity of this protein, causing abnormal pain perception. By restoring normal KCC2 activity we could potentially prevent pain hypersensitivity." Dr. De Koninck and researchers at Université Laval are testing new molecules capable of preserving KCC2 functions and thus preventing hyperalgesia.

The KCC2 pathway appears to apply to short-term as well as to long-term morphine administration, says Dr. De Koninck. "Thus, we have the foundation for new strategies to improve the treatment of post-operative as well as [chronic pain](#)."

Dr. Salter adds, "Our discovery could have a major impact on individuals with various types of intractable pain, such as that associated with cancer or nerve damage, who have stopped morphine or other

opiate medications because of pain hypersensitivity."

Cost of pain

Pain has been labelled the silent health crisis, afflicting tens of millions of people worldwide. Pain has a profound negative effect on the quality of human life. Pain affects nearly all aspects of human existence, with untreated or under-treated pain being the most common cause of disability. The Canadian Pain Society estimates that chronic pain affects at least one in five Canadians and costs Canada \$55-60 billion per year, including health care expenses and lost productivity.

"People with incapacitating pain may be left with no alternatives when our most powerful medications intensify their suffering," says Dr. De Koninck, who is also Director of Cellular and Molecular [Neuroscience](#) at Institut universitaire en santé mentale de Québec.

Dr. Salter adds, "Pain interferes with many aspects of an individual's life. Too often, patients with chronic pain feel abandoned and stigmatized. Among the many burdens on individuals and their families, chronic pain is linked to increased risk of suicide. The burden of chronic pain affects children and teens as well as adults." These risks affect individuals with many types of pain, ranging from migraine and carpal-tunnel syndrome to cancer, AIDS, diabetes, traumatic injuries, Parkinson's disease and dozens of other conditions.

Provided by Laval University

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