- Analgesic

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Paracetamol is an over-the-counter medicine for pain relief

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HEALTH

We may finally know how paracetamol works

WORDS CLARISSA BRINCAT

Acetaminophen is widely used to relieve pain, but exactly how it works has long been a mystery. Now, a new study suggests that a key byproduct of acetaminophen may block pain signals at the nerves before they can reach the brain. Acetaminophen, also called paracetamol, is broken down by the liver into a compound called 4-aminophenol, which travels through the bloodstream to different organs. There, an enzyme links it with a fatty acid to produce AM404.

Previous research found that AM404 can act in the central nervous system, the brain and spinal cord. But the new study reveals that AM404 also affects the peripheral nervous system, which is where pain signals originate. "Even though we've been using paracetamol for the management of pain for more than 130 years, we still don't fully understand how the drug works," said Nial Wheate, a professor of pharmaceutical chemistry at Macquarie University in Australia, who wasn't involved in the study. One widely held theory was that acetaminophen stopped the body from making prostaglandins, which can trigger pain and inflammation. "If the results of this study are confirmed," said Wheate, "then it significantly changes our understanding of the drug."

However, the new study was in rats, so the findings may not apply in humans. To test the effects of AM404, the scientists applied the compound to sensory neurons taken from newborn rats. They found that it blocks sodium channels, proteins that normally allow charged sodium particles to pass in and out of cells, which are essential for generating and transmitting pain signals. By blocking these channels, AM404 keeps the neurons from sending pain messages to the brain. Other byproducts of acetaminophen had no such effect.

The researchers also injected AM404 into the paws of rats and tested their responses to painful stimuli. The treated paws became less sensitive to heat and pressure, with the strongest effect appearing about an hour after the injection. Importantly, the pain relief was limited to the site of the injection, leaving the other paw unaffected.

While the findings may not change how acetaminophen is currently used to treat pain, they could influence the development of next-generation painkillers that are potentially safer. Acetaminophen overdoses can damage the liver and are responsible for 56,000 emergency visits a year in the US. "Whole families of new drugs could be designed based around blocking sodium channels. These new drugs could be both more effective and safer than not just paracetamol, but other painkillers like ibuprofen or opioids," Wheate said.

Looking ahead, the researchers hope to design improved versions of AM404 that are more chemically stable and optimised to work in the peripheral nervous system. They also plan to test whether these compounds can help with chronic or nerve-related pain, where standard treatments often fall short. Another important next step is to assess the safety and therapeutic potential of AM404 in greater detail. This involves understanding how it's broken down and distributed in the body and whether it might affect any other organs.