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First study to reveal how paracetamol works could lead to less harmful pain relief medicines

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Researchers at King's College London have discovered how one of the most common household painkillers works, which could pave the way for less harmful pain relief medications to be developed in the future.

Paracetamol, often known in the US and Asia as acetaminophen, is a widely-used analgesic (painkiller) and the main ingredient in everyday medications such as cold and flu remedies. Although discovered in the 1890s and marketed as a painkiller since the 1950s, exactly how it relieves pain was unknown.

This study, funded by the UK Medical Research Council (MRC) and published online today in *Nature Communications*, shows for the first time the principal mechanism of action for one of the most-used drugs in the world.

The researchers from King's, with colleagues from Lund University in Sweden, have identified that a protein called TRPA1, found on the surface of nerve cells, is a key molecule needed for paracetamol to be an effective painkiller.

Dr David Andersson, from the Wolfson Centre for Age Related Diseases at King's, said: 'This is an extremely exciting finding, which unlocks the secrets of one of the most widely-used medicines, and one which could impact hugely on the development of new pain relief drugs.

'Paracetamol is the go-to medicine for treating common aches and pains, but if the recommended dose is significantly exceeded it can lead to fatal complications.

'So now we understand the underlying principal mechanism behind how this drug works, we can start to look for molecules that work in the same way to effectively relieve pain, but are less toxic and will not lead to serious complications following overdose.'

The team of researchers used a 'hot-plate' test to observe the effects of paracetamol in mice. This involved measuring the number of seconds it takes for a mouse to withdraw its paw from a slightly hot surface. They found that paracetamol increased the time it took for mice to withdraw their paw, showing that the drug reduced the heat-induced pain.

The scientists then carried out experiments to observe what happened when a protein called TRPA1 was not present at all in the mice. They found that when they removed the TRPA1 protein and repeated the hot-plate test, the paracetamol had no analgesic effect. This identifies the protein as a key molecule needed for paracetamol to be an effective painkiller.

However, paracetamol on its own does not activate the TRPA1 protein. The study showed that when paracetamol is administered, a break-down product called NAPQI is formed in the spinal cord (where 'painful' information is processed). This product is also formed in the liver and is responsible for the toxic side effects seen following overdoses.

Furthermore, they demonstrated that other compounds that, unlike NAPQI, are not toxic can activate TPRA1 in the spinal cord when injected into mice. Because these compounds are not reactive, they are less likely to be harmful.

Professor Stuart Bevan, co-author from King's, said: 'What we saw happening in the mice was that the break-down product formed from paracetamol in turn stimulates a protein found on the surface of nerve cells called TRPA1. When this protein was activated, it appeared to interfere with the transmission of information from that nerve cell to other nerve cells, which would normally send a signal up to the brain, signalling pain. So in this case the NAPQI product that was formed from paracetamol acted on the TRPA1 protein to reduce transmission of information from pain-sensing nerves to the brain.

'These results are surprising because previous studies have shown that TRPA1 can actually produce pain, coughs and hypersensitivities – it is the receptor for many common irritants like onion, mustard and tear gas. So our discovery shows for the first time that the opposite is in fact true – this protein is a novel mechanism of action for a painkiller.'

The researchers say that if they can identify other analgesic compounds similar to paracetamol that use the same TRPA1 pathway to prevent pain signals sent by nerve cells to the brain, it is possible that they can find a compound that does not have toxic effects and will reduce the risk of overdose.

Dr Andersson concludes: 'This study validates TRPA1 as a new target for pain relief drugs. Many targets have been identified in the past, but as paracetamol is a medicine that we know works well in humans, this gives us a head-start in looking for effective molecules that utilise the same pathways but are less harmful.'

Provided by King's College London