Research into opioid painkillers could provide clues for safer drug development

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Researchers have taken a step closer to understanding the body's response to opioid painkillers such as morphine and fentanyl, which could lead to the development of safer opioid drugs.

Opioids are a class of powerful painkillers used to treat moderate to

severe pain. They act on the nervous system, stimulating opioid receptors which then block pain. But continued use can lead to physical dependence and withdrawal symptoms, partly because the body's tolerance builds up quickly and pain control diminishes.

Now, research published in *Nature Communications* has identified the specific molecular mechanisms in the body which respond to the opioids and cause this increasing tolerance.

Dr. Alexis Bailey at St George's, University of London was part of the research team, which was led by Professor Schulz of Jena University Hospital, Germany.

The researchers developed genetically modified mice that lacked phosphorylation sites of the "mu" (μ) opioid receptor, the target of opioid painkillers in the central nervous system. These mice subsequently built up very little tolerance to opioids such as fentanyl and morphine. As a result, the painkilling effect of these drugs was dramatically increased.

But the side effects of the drugs, such as constipation, respiratory depression and withdrawal symptoms, remained unchanged or were exacerbated.

The researchers' findings show that tolerance and dependence are two dissociable phenomena governed by separate molecular mechanisms.

While it had been demonstrated that the "mu" phosphorylation sites played a role in opioid tolerance in cells, this is the first time it has been proven in animal models.

In 2017, 23.8 million prescriptions were dispensed for opioids such as tramadol in England – one for every two adults. Hospital admissions in

the UK involving opioid overdoses have almost doubled in a decade to 2017.

Dr. Alexis Bailey of St George's, University of London, who worked on the research along with Professor Stefan Schulz of Jena University Hospital, Germany, said: "So-called 'safe opioids' that are less likely to result in dependence, tolerance and risk of accidental overdose have been the Holy Grail of opioid research. This study takes us a step closer to understanding the underlying molecular mechanisms of how they work on the body, which is an absolute prerequisite to devising new strategies for drug development."

More information: A. Kliewer et al. Phosphorylation-deficient G-protein-biased μ-opioid receptors improve analgesia and diminish tolerance but worsen opioid side effects, *Nature Communications* (2019). DOI: 10.1038/s41467-018-08162-1

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