Scientists reveal new insights and possible solutions for opioid epidemics using machine

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Mount Sinai researchers have identified unique structural, biological and chemical insights in the way different opioid drugs activate the receptors and specific signaling pathways responsible for the drug's beneficial and adverse effects, according to a study to be published in Nature's *Scientific Reports*.

Opioid overdoses are the leading cause of accidental death in the United States. The findings of this study may provide a blueprint for designing improved painkillers.

"These new insights will provide a roadmap to develop a new class of drugs that are non-addictive and less harmful for patients," said Marta Filizola, PhD, Professor of Pharmacological Science and Professor of Neuroscience, Dean of The Graduate School of Biomedical Sciences at Icahn School of Medicine at Mount Sinai, and lead investigator of the study. "These insights may help us engineer new painkillers with reduced side effects, particularly respiratory depression. An alternative, non-addictive medication for chronic pain will help us combat the ongoing national crisis of addiction to opioid drugs and the devastating overdose epidemic deriving from it."

There have been many attempts to develop better opioid drugs but this has been largely unsuccessful due to incomplete understanding of the molecular signatures underlying the analgesic effects as opposed to the unwanted side effects. Potent opioid drugs that are often tied to fatal overdoses (e.g., heroin, fentanyl, or carfentanil) work by binding to opioid receptors in the nervous system. These drugs also provoke dopamine release, which causes euphoria leading to addiction and inhibits nerve cells in a region of the brain that regulates breathing, which can lead to respiratory depression and accidental death by overdose.

The therapeutic effect of opioid drugs is mainly attributed to mu-opioid receptor (MOR) activation leading to G protein signaling, meaning that the drug binds to the MOR receptor and causes a change in its molecular structure, which then activates a protein called the G protein. However, the drug's side effects have mostly been linked to a different process known as ?-arrestin signaling, which plays a role in the regulation of these receptors. To shed light on this, the researchers carried out molecular dynamics simulations in mouse models of MOR bound to a classical opioid drug (morphine) or a potent G protein-biased agonist (TRV-130) that is currently being evaluated in human clinical trials for its potent analgesic effect with less respiratory depression and constipation than morphine.

The results of rigorous machine learning analyses of these simulations revealed unique structural, dynamic, and kinetic insights that have a direct utilization in the design of improved therapeutics targeting MOR.

Provided by The Mount Sinai Hospital

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